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CARCINOGENESIS ABSTRACTS

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ABBREVIATIONS

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LANGUAGE of the article is indicated in parentheses after the title and is represented by a three-letter code. The source for these codes is *MARC Manuals Used by the Library of Congress*, pages 183-187.

ABBREVIATIONS used in abstracts:

A	angstrom(s)
ACTH	adrenocorticotropic hormone
ADP	adenosine diphosphate
AMP	adenosine monophosphate
ATP	adenosine triphosphate
approx	approximately
av	average
BCG	bacillus Calmette-Guerin
bid	twice daily
C	degree(s) centigrade
cal	calorie(s)
kcal	kilocalorie(s)
cc	cubic centimeter(s)
Ci	curie(s)
mCi	millicurie(s)
μCi	microcurie(s)
cm	centimeter(s)
CNS	central nervous system
cpm	counts per minute
DNA	deoxyribonucleic acid
ED_{50}	median effective dose
EDTA	ethylenediamine tetraacetic acid
g	gram(s)
kg	kilogram(s)
mg	milligram(s)
μg	microgram(s)
Hb	hemoglobin
hr	hour(s)
ia	intra-arterial
id	intradermal
IgA	Immunoglobulin A
IgB	Immunoglobulin B
IgG	Immunoglobulin G
IgM	Immunoglobulin M
ILS	increased life span
im	intramuscular
ip	intraperitoneal
IU	International Unit(s)
iv	intravenous
Km	Michaelis constant
LD	lethal dose
LD_{50}	median lethal dose
M	molar
μM	micromolar
mOsm	milliosmolar
max	maximum
mEq	milliequivalent(s)
min	minute(s)
ml	milliliter(s)
μl	microliter(s)
mm	millimeter(s)
mo	month(s)
mol wt	molecular weight
N	normal concentration
NAD	nicotinamide adenine dinucleotide
NADH	reduced nicotinamide adenine dinucleotide
NADP	nicotinamide adenine dinucleotidephosphate
NADPH	reduced nicotinamide adenine dinucleotidephosphate
NCI	National Cancer Institute
NIH	National Institutes of Health
PAS	periodic acid-Schiff
po	orally
ppb	parts per billion
ppm	parts per million
qid	four times daily
qod	every other day
QO_2	oxygen quotient
R	roentgen
RBC	red blood cells (erythrocytes)
RNA	ribonucleic acid
rpm	revolutions per minute
sc	subcutaneous
sec	second(s)
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
soln	solution
TCD	tissue culture dose
TCD_{50}	median tissue culture dose
tid	three times daily
UV	ultraviolet
WBC	white blood cells (leukocytes)
wk	week(s)
wt	weight
X	times
yr	year(s)

3-4801 **Aspects in Carcinogen Bioassay.** (Eng) Sontag, J. M. (Div. Cancer Cause and Prevention, NCI, ethesda, MD, 20014). *In: Human Risk Assessment. Proceedgs of the Cold Spring Harbor Conferences on Cell Proliferan.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold pring Harbor: Cold Spring Harbor Laboratory): Origins of uman Cancer. Vol. 4 (Book C), 583 pp.; 1327-1338; 1977.

actors to be considered in the design and conduct of ng-term carcinogen bioassays are reviewed. These factors clude the following: (1) selection of a chemical compound a form that will reflect the danger to humans; (2) chemical uality control; (3) choice of animal for bioassay; (4) proper re of the animal and its surroundings; (5) genetic composion of the animal; (6) safety and health of laboratory person-el; (7) establishment of the max tolerated dose that can be dministered during a chronic toxicity study; (8) parameters f the chronic study such as animal group size, treatment ose levels, route and mode of administration, and the detail f pathologic examination; (9) the use of positive control; and 10) method of data collection. (9 refs.)

8-4802 **Identifying and Defining Chemical Carcinogens.** (Eng) Saffiotti, U. (Experimental Patholoy Branch, Carcinogenesis Program, Div. Cancer Cause and revention, NCI, NIH, Bethesda, MD, 20014). *In: Human isk Assessment. Proceedings of the Cold Spring Harbor Conerences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Vinsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book C), 83 pp.; 1311-1326; 1977.

Changing parameters in toxicological studies are reviewed, nd the application of these studies to chemical carcinogenesis is discussed. Traditionally, toxicology was concerned with ubstances producing early recognizable effects, the intensity f which was directly correlated with the intensity of expoure. The manifestations of the toxicity were due to altered unctional products, degenerative changes, or target cell eath. Carcinogenic toxicity, however, is characterized by a elay in the appearance of toxic effects; and although the requency of tumor incidence (injury) is directly correlated with the intensity of exposure, the intensity of the induced athology (tumor growth and spread) is independent of the ntensity of exposure. Furthermore, the manifestations of toxicity are due to the proliferative response of a new altered cell opulation. The application of this new toxicology include epidemiologic studies of cancer prevalence in humans exposed to potential carcinogens, experimental long-term studies of cancer induction in animals exposed to test substances, and experimental short-term studies of neoplastic transformation, mutagenic activity, and chemical interactions with target macromolecules. (103 refs.)

78-4803 **Chronic Toxicity and Carcinogenicity Guidelines.** (Eng) Page, N. P. (Natl. Inst. Occupational Safety and Health, Parklawn Building, Room 8A-30, 5600 Fishers Lane, Rockville, MD, 20857). *J Environ Pathol Toxicol* 1(2): 161-182; 1977.

Protocols and guidelines for chronic toxicity and carcinogenesis tests that have been developed by national and international organizations are reviewed with respect to two factors: the potential for standardization and the assessment of issues of greatest concern. Of the major design aspects, animal models, route of exposure, dose selection, pathology examination, and reporting requirements are the most controversial. Complete standardization of protocols is not considered desirable because test objectives may differ and overly rigid protocols would be likely to stifle development of improved methodology. One of the greatest dilemmas is the extent of pathology that should be required in routine bioassays. Although a thorough microscopic examination is obviously desirable, the increased requirements for testing chemicals using the extensive pathology protocols now in existence has created a demand exceeding available scientific manpower. The past few years have seen great improvements in standard bioassays, but refinements are still needed to provide for: the use of dose level(s) that will allow for assessment of dose response and altered physiology; comparative/correlative metabolism studies; and the routine use of a defined, contaminant-free diet. (48 refs.)

78-4804 **Metabolic Activation of Carcinogens.** (Eng) Irving, C. C. (Veterans Admin. Hosp., Dept. Urology, Univ. Tennessee Center Health Sciences, Memphis, TN). *In: Carcinogens: Identification and Mechanisms of Action. Proceedings of the Thirty-First Annual Symposium on Fundamental Cancer Research Held at Houston, Texas, 1-3 March 1978.* University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, NCI, American Cancer Society. (Austin, Texas). 13 pp.; 1978. (no refs)

78-4805 **When Is the Extrapolation of Animal Carcinogenesis to Man Inappropriate? (Letter to Edi-**

tor). (Eng) Gross, P. (Industrial Health Foundation, Inc., 5231 Centre Ave., Pittsburgh, PA, 15232); Braun, D. C. *J Occup Med* 20(4): 236-240; 1978.

Positive carcinogenesis test results in animals can be extrapolated to humans except when the carcinogenic effect results from physical rather than chemical induction or when the administrative route was grossly inappropriate. Experiments in which there were ip injections or pleural implantations of large fibers in rats are presented as examples of these exceptions. (13 refs)

78-4806 **Inhibitors of Chemical Carcinogenesis.** (Eng) Wattenberg, L. W. (Dept. Laboratory Medicine and Pathology, Univ. Minnesota, Minneapolis, MN, 55455); Lam, L. K.; Speier, J. L.; Loub, W. D.; Borchert, P. *In: Mechanisms of Carcinogenesis. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book B), 699 pp.; 785-799; 1977.

The following low-toxicity inhibitors of chemical carcinogenesis are discussed: butylated hydroxyanisole, butylated hydroxytoluene, ethoxyquin, disulfiram and related compounds, benzyl isothiocyanate and related compounds, selenium compounds, cysteamine hydrochloride, and various inducers or microsomal mixed-function oxidase activity. The latter include polycyclic hydrocarbons, polychlorinated biphenyls, phenobarbital β-napthoflavone, phenothiazine, α-benzene hexachloride, chlordane, and quercetinpentamethyl ether. These compounds have broad structures, which indicate that a substantial number of other, as yet unidentified, inhibitors probably exist. Before an inhibitor can be considered for use in diminishing the impact of chemical carcinogens on human populations, it should be shown to have trivial or no toxicity, and evidence should exist that its intake by a particular population results in a low cancer incidence. Less absolute requirements regarding a lack of toxicity might be justified for an inhibitor that is to be used in populations with elevated exposures to chemical carcinogens. (32 refs.)

78-4807 **Species Differences in Carcinogenesis Testing.** (Eng) Rall, D. P. (Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC, 27709). *In: Human Risk Assessment. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book C), 583 pp.; 1383-1390; 1977.

Problems associated with the extrapolation of carcinogenesis test data from small animals to humans are reviewed, and the ability of animal studies to predict human toxic and carcinogenic responses is discussed. Differences between laboratory animals and man include different metabolic patterns and cell turnover time, different life spans, differences in body sizes resulting in different distribution of chemicals in animals, number of cells at risk, extrapolation from a genetically homogeneous population to a heterogeneous one and from a well-fed one to one with various nutritional statuses, and (since test animals receive basically the pure compound) the problem of synergistic toxicity. However, the only well-controlled comparative study indicated a strong correlation between the toxicity of 17 anticancer drugs in man and laboratory animals. In this experiment, the clinical situation and dosimetry in man were duplicated in the laboratory animals. It is suggested that carcinogenic testing situations in laboratory animals approximate the conditions to which humans will likely be exposed. (10 refs.)

78-4808 **The Applicability of Fish to Carcinogenesis Studies.** (Hun) Lapis, K. (I. sz. Korbonctani Intezet, Semmelweis Orvostudomanyi Egyetem, Budapest, Hungary); Simon, K.; Szende, B. *Magy Onkol* 22(2): 75-86; 1978.

Although the testing of substances for carcinogenic activity is expensive and time-consuming, in vitro short-term tests cannot be substituted for in vivo animal experiments traditionally performed with rodents. Fish are more promising models for carcinogenicity studies than rodents since they require a shorter time for tumor development, and the studies are less expensive. The results obtained with both fish and rodents are comparable. Furthermore, the use of both rodents and fish would fulfill the requirement that tests be performed on more than one species. Under certain circumstances fish can also be used to screen carcinogens. The results of carcinogenesis experiments with fish in the literature are presented. (34 refs)

78-4809 **The *Salmonella*/Microsome Mutagenicity Test: Predictive Value for Animal Carcinogenicity.** (Eng) McCann, J. (Dept. Biochemistry, Univ. California, Berkeley, CA, 94720); Ames, B. N. *In: Human Risk Assessment. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book C), 583 pp.; 1431-1450; 1977.

The predictive value of the *Salmonella*/microsome mutagenicity assay for animal carcinogenicity is discussed. Testing of hundreds of chemicals has revealed greater than millionfold range of mutagenic potency of carcinogens in the assay. Attempts are being made to determine the relationship between mutagenic and carcinogenic potency, but information on the latter is sparse. The assay was validated with about 300 organic chemicals that have been tested in conven-

tional animal carcinogenicity tests. Most (157/175) of the carcinogens were mutagenic in the assay, and 94/104 of the noncarcinogens were nonmutagens. With further improvements in both the tester strains and the metabolic activation system, the assay is expected to detect at least 95% of all carcinogens. The remaining percent will probably fall into the hormone and promoter category or will be a class of mutagens unique to animal cells. False positives may be caused by bacterial activation of chemicals by enzymes that are not functional in animals, by limitations of animal carcinogenicity tests, and by mutagenic impurities. Several chemicals used in consumer products, including two hair dye components, 4-nitro-o-phenylenediamine and 2-nitro-p-phenylenediamine, and tris-(2,3-dibromopropyl)phosphate, the main flame retardant in children's polyester pajamas, were detected as mutagens by the assay and have since proved to be carcinogenic. It is suggested that damage to DNA by environmental mutagens initials most human cancers, as well as genetic defects. The results of these studies support the theory that radiation and chemical carcinogens cause cancer through somatic mutation. (49 refs)

78-4810 **Epidemiology, Multistage Models, and Short-term Mutagenicity Tests.** (Eng) Peto, R. (Regius Dept. Medicine, Oxford Univ., Oxford OX2 6HE, England). *In: Human Risk Assessment. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book C), 583 pp.; 1403-1428; 1977.

The value of multistage models in calculating cancer risks is reviewed. Most multistage models indicate that the final cancer incidence rate is the arithmetic product of more than one term, each of the different terms being dependent on different causative agents or processes. If this is so, cancer incidence could be reduced by decreasing the levels of exposure to a compound (eg, an environmental pollutant) or by manipulating the other unknown factors involved and so disrupting the sequence of events. Mutagenicity studies could play a key role in identifying these factors. In reviewing multistage models, lung cancer, epidemiology, and suggestions that almost all carcinogens are mutagens, three conclusions were reached. (1) Multistage models do not necessarily require a large number (approx 6) of distinct rate-limiting cellular changes as is often assumed to take place during epithelial cell transformation (2). Although the mechanisms of induction of most carcinomas may be similar, they probably differ fundamentally from the mechanisms of induction of leukemias, sarcomas, etc; thus much of the research into leukemia or sarcoma viruses may be irrelevant to human carcinomas. (3) Some of the extrinsic rate-determining causes of human lung cancer are not the direct- or indirect-acting agents detected by in vitro mutagenicity tests; this is probably true for other carcinomas as well. (45 refs.)

78-4811 **Safeguarding the Quality of Microbiological Mutagenicity Testing of Foreign Substances in Routine Laboratory.** (Ger) Norpoth, K. (Munster, W. Germany). *Staub-Reinhalt Luft* 38(6): 235-239; 1978.

General methodological and statistical questions relevant to the use of bacteria in mutagenicity tests of environmental compounds are discussed. The probability of carcinogenic effects can be assessed from the results of mutagenicity tests on microorganisms such as *Salmonella typhimurium*. The development of routine bacterial mutagenicity tests requires standardization, quality control, and statistical validation of the results. The prerequisites include positive and negative controls, continuous checks on the indicator bacteria, constant activity of the mammalian oxygenase used, species-specificity of the oxygenase, and attention to the influence of the solvent. 3,4-benzo(a)pyrene, aflatoxin B_1, vinyl chloride, diaminotoluene, known carcinogens, and *bis*(chloroethyl)ether, a suspected carcinogen, were found to induce mutations in microorganisms. (10 refs.)

78-4812 **Identification of Carcinogens by Mutagen Testing in *Drosophila*: The Relative Reliability for the Kinds of Genetic Damage Measured.** (Eng) Vogel, E. (Dept. Radiation Genetics and Chemical Mutagenesis, Sylvius Lab., State Univ. Leiden, Leiden, Netherlands). *In: Human Risk Assessment. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A.; eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book C), 583 pp.; 1483-1499; 1977.

The usefulness of mutagen testing of *Drosophila* for the identification of carcinogens is discussed. Identification is largely dependent on the genetic end point used as a diagnostic criterion. Comparative experiments have shown the existence of two effect levels; ie, concentrations required to raise the number of point mutations (recessive lethals) significantly are considerably lower than those needed for the chromosome breakage effect. This explains the superior discriminating power of recessive-lethal assays over assays of chromosome breakage. *Drosophila* can execute the essential activation steps required to convert precarcinogens to highly reactive species. Intragonadal metabolism plays an important role in this activation, and particular attention must be paid to metabolically active germ-cell stages when testing precarcinogens in *Drosophila*. The larvae also have the enzymatic machinery needed to carry out the essential activation steps, and they are more sensitive to mutagens than the adult fly. Some problems have been encountered in this system, including deactivation of some compounds before the genetic target is reached, differences in mutagenicity depending on route of application, and the nonmutagenicity of the carcinogenic polycyclic hydrocarbons and aromatic amines. The latter problem may be overcome by developing mutagen-sensitive

strains. It is proposed that the *Drosophila* assay system be used as an exploratory screening phase and also in in-depth analyses of potent mutagens. (39 refs)

78-4813 **Estimation of "Safe Doses" in Carcinogenic Experiments.** (Eng) Hartley, H. O. (Inst. Statistics, Texas A & M Univ., College Station, TX, 77843); Sielken, R. L. *J Environ Pathol Toxicol* 1(2): 241-278; 1977.

A multiparametric model approach to estimating safe doses in carcinogen-testing experiments is described. It is comprised of an adequately large number of parameters to allow for differences in the idiosyncracies of suspected carcinogens, and the host species and, to a limited degree, for variations in the experimental protocols. The same computer program can cover the analysis of an experiment in which latent periods have been recorded as well as experiments in which only tumor incidence rates have been recorded, or mixtures of the two. The max likelihood estimation procedure has asymptotic optimality properties. It uses the latest techniques of convex programming. Although the model is multiparametric, it is of the form of the product model for age-specific hazard rates, a form that is now widely accepted. No estimates of safe doses can be made if the spontaneous incidence rate is zero, if the experimental dose levels are too small, and if no tumors have been observed. If the experimental doses are too small and the tumor incidence rates are comparable with the spontaneous rate, the estimation procedure has extremely large errors. The statistical analyses are given in detail in a series of appendices. (32 refs)

78-4814 **Aspects of the Hartley-Sielken Approach for Setting "Safe Doses" of Carcinogens.** (Eng) Mantel, N. (Biostatistics Center, George Washington Univ., Bethesda, MD, 20014). *In: Human Risk Assessment. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book C), 583 pp.; 1397-1401; 1977.

Various requirements imposed by the Hartley-Sielken approach to establishing safe dose levels of carcinogens for human exposure are reviewed. Since this approach depends on the fitting of high-degree polynomials into the calculations, a sufficiently large number of dose levels must be explored. Furthermore, because the data are going to be segmented, sufficiently large numbers of animals must be employed at each dose level. Finally, the resulting data must show some frequency of tumor occurrence. A comparison between the requirements of this method and a one-hit model is presented. (6 refs.)

78-4815 **Comparisons of Carcinogenic and Mutagenic Potency.** (Eng) Meselson, M. (Biological Labs., Harvard Univ., Cambridge, MA, 02138); Russell, K. *In: Human Risk Assessment. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book C), 583 pp.; 1473-1481; 1977.

Fourteen compounds that are both carcinogenic and mutagenic were examined to determine if there is a quantitative relationship between carcinogenic and mutagenic potency. These compounds were aflatoxin B_1, 4-aminobiphenyl, benzidine, benzo(a)pyrene, dibenz(a,h)anthracene, diethylnitrosamine, dimethylnitrosamine, di-n-butylnitrosamine, 4,4′-methylene-bis-2-chloroanaline, methyl methanesulfonate, β-naphthylamine, N-nitrosomethylurea, 1,3-propane sultone, and sterigmatocystin. The carcinogenic potency of most of these compounds in laboratory rodents was approx equal to their mutagenic potency in *Salmonella typhimurium*, using the definitions of the two potencies given. For several N-nitroso compounds, however, carcinogenic potency was considerably greater than mutagenic potency. It is suggested that the carcinogenic potency of a mutagenic compound for humans may be roughly equal to that in rodents if the carcinogenic potencies are expressed in terms of the av normal life-spans of the respective species. With this condition, it is concluded that the Ames *Salmonella* test is sufficiently sensitive to analyze complex mixtures in order to identify mutagenic compounds that may be responsible for the induction of an important fraction of human cancers. (36 refs.)

78-4816 **Ultimate Chemical Carcinogens as Reactive Mutagenic Electrophiles.** (Eng) Miller, J. A. (McArdle Lab. Cancer Res., Univ. Wisconsin Medical Center, Madison, WI, 53706); Miller, E. C. *In: Mechanisms of Carcinogenesis. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book B), 699 pp.; 605-627; 1977.

Available data indicate that the ultimate carcinogenic forms of most chemical carcinogens are strong electrophilic reactants that differ from the normal cellular electrophiles in that they generally attack cellular nucleophiles nonenzymatically and with relatively little imination. In this light, the metabolic activation of 2-acetylamino fluorene, N-methyl-4-aminoazobenzene, other amines and amides, the pyrrolizidine alkaloids, cycasin, and safrole is reviewed. The metabolic activation of aflatoxin B_1 (AFB_1) and the nature of the major covalent DNA and RNA adducts of AFB_1 formed in vitro and in vivo are also discussed. The potent carcinogenicity of AFB_1 2,3-dichloride for the skin and lungs of mice and for the sc tissue of rats provides support for the conclusion that

AFB_1 2,3-oxide is a major ultimate carcinogenic metabolite of AFB_1. The electrophilic character of ultimate chemical carcinogens provides the basis for at least three types of pre-screens for the detection of potential carcinogens. Thus, the electrophilic nature of the parent compound and of known or likely metabolites can serve as an early warning that these compounds may have carcinogenic activity. (90 refs.)

78-4817 **Standard-Setting for Nitrites and Nitrosamines.** (Eng) Lijinsky, W. (Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21501). *In: Human Risk Assessment. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book C), 583 pp.; 1807-1811; 1977.

Several methods for reducing human exposure to nitroso compounds are proposed. These methods include reduction of the excessive use of nitrosatable amines, reduction of the amount of residual nitrite allowable in cured meats, and the administration of drugs that can react with nitrites in the stomach by injection rather than po. Adherence to these suggestions may reduce cancer incidence over the next few decades. (5 refs.)

78-4818 **Nitrate and the Etiology of Gastric Cancer.** (Eng) Tannenbaum, S. R. (Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, MA, 02139); Archer, M. C.; Wishnok, J. S.; Correa, P.; Cuello, C.; Haenszel, W. *In: Human Risk Assessment. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book C), 583 pp.; 1609-1625; 1977.

Two models of gastric cancer are proposed based on evidence gathered in Colombia, South America, and laboratory tests of these models are described. A survey of water supplies in a high-risk area in Colombia has shown high concentrations of nitrates in wells. In this region, the disease progresses from normal mucosa to superficial gastritis, chronic atrophic gastritis, gastritis with intestinal metaplasia, and, finally, gastric cancer. By age 25, > 75% of the population in the high-risk area suffers from gastritis, whereas in the low-risk area the population appears to be free of gastric pathology. Two models emerge from these observations: (1) an agent in the environment, possibly an N-nitroso compound, leads to gastritis, which naturally progresses to intestinal metaplasia and then to cancer; (2) gastritis leads to elevation of the stomach pH and, concomitantly, to establishment of a microbial flora capable of nitrate reduction. This process, in turn, leads to a steady formation of carcinogenic N-nitroso compounds, which leads to gastric cancer. At present, there is not enough evidence to decide between these two models. Laboratory studies involving saliva and stomach acid indicate that bacteria in the stomach of an individual with gastritis or intestinal metaplasia play the dual roles of nitrite former and nitrosation catalyst. Other studies have disclosed the formation of cyanamides from primary and secondary amines in human saliva. Mixing of these compounds with the stomach contents would result in the formation of highly mutagenic and carcinogenic N-nitrosocyanamides. (46 refs)

78-4819 **Nitrosamines and Their Precursors in Food.** (Eng) Lijinsky, W. (Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21501); Taylor, H. W. *In: Human Risk Assessment. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book C), 583 pp.; 1579-1590; 1977.

The carcinogenicity of N-nitroso compounds and their formation from food components are discussed. More than 120 N-nitroso compounds have been synthesized and tested by long-term administration of small doses to rats. Three-quarters of these compounds were found to be carcinogenic. Two compounds induced tumors in > 20 animal species. It is improbable that any species is refractory to N-nitroso compounds. These compounds are formed easily from nitrites and amines and they probably exist in the human environment, particularly in foods that contain nitrite; eg, cured meats. Nitrite is also formed by reduction of the nitrate in vegetables, eg, spinach and beets, and water. Preformed nitrosamines found in food are usually present at low levels (10 ppb). A more important source of nitrosamines is from ingested amines and nitrite. A majority of drugs and medicines are nitrosatable amines, as are agricultural chemicals, food constituents, and food additives. In tests in which secondary and tertiary amines plus nitrite were given to rats in the drinking water, several amines, including aminopyrine and Methapyrilene produced a significant incidence of malignant tumors. (18 refs)

78-4820 **Evidence for the Formation of Electrophilic Metabolites from N-nitroso Compounds.** (Eng) Magee, P. N. (Fels Res. Inst., Temple Univ. Sch. Medicine, Philadelphia, PA, 19140). *In: Mechanisms of Carcinogenesis. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book B), 699 pp.; 629-637; 1977.

Evidence that administration of N-nitroso carcinogens to animals gives rise to the same type of electrophilic alkylating intermediate in the body is presented. There appears to be

no species among those tested so far, including mammals, birds, amphibia, and fish, that has proved resistant to carcinogenesis by N-nitroso compounds. Furthermore, there appear to be sufficient similarities in the patterns of tumor induction by these carcinogens to warrant the conclusion that their molecular mechanisms are probably similar. In contrast to the nitrosamides, the nitrosamines are essentially inactive as mutagens unless a metabolic activating system is available. Studies of the metabolism of dimethylnitrosamine indicate that the methylating intermediate must pass through the vascular walls of the liver and other organs capable of metabolizing the nitrosamine and methylate the RBC. The available evidence is consistent with the hypothesis that the carcinogenic N-nitroso compounds, symmetrical dialkylhydrazines, azo- and azoxyalkanes, and derivatives of methylazoxymethanol produce their biological effects by the reaction of cellular constituents with electrophilic alkylating intermediates. (45 refs.)

78-4821 **N-Nitrosodimethylamine.** (Eng) IARC Working Group (Lyon, France). *In: Some N-Nitroso Compounds.* Magee, P. N., Chairman (International Agency for Research on Cancer: Switzerland): IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 17, 365 pp.; 125-175; 1978.

Experimental findings on the carcinogenicity of N-nitrosodimethylamine (NDMA) are reviewed. Until April 1976, NDMA was used as an intermediate in the production of rocket fuel; currently, it is used solely for research purposes. This compound is carcinogenic in mice, rats, Syrian golden hamsters, Chinese hamsters, European hamsters, guinea pigs, rabbits, ducks, mastomys, various fish, newts, and frogs. It produces benign and malignant tumors, mainly of the liver, kidney, and respiratory tract, following administration by various routes. NDMA is mutagenic in various strains of bacteria and in *Drosophila*, and it induces chromosome aberrations in Chinese hamster cells. Although no human case reports or epidemiological studies were available for analysis, there is sufficient experimental evidence of the carcinogenicity of NDMA. It is suggested that NDMA should be regarded as if it were carcinogenic to humans. (274 refs.)

78-4822 **N-Nitrosodiethylamine.** (Eng) IARC Working Group (Lyon, France). *In: Some N-Nitroso Compounds.* Magee, P. N., Chairman (International Agency for Research on Cancer: Switzerland): IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 17, 365 pp.; 83-124; 1978.

Biological data relevant to an evaluation of carcinogenic risk to humans are presented for N-nitrosodiethylamine (NDEA). The compound has been reported to occur in the air (one area of Baltimore), tobacco smoke, well-water, the waste water from 2/19 chemical plants, various types of food, animal feed, and alcoholic beverages. NDEA is carcinogenic in all animal species tested: mice, rats, rabbits, dogs, gerbils, pigs, monkeys, hedgehogs, various fish, frogs, birds, and Syrian golden, Chinese, and European hamsters. It induces benign and malignant tumors after administration by various routes, including ingestion, parenteral injection, inhalation, and rectal instillation. The major target organs are the liver, respiratory and upper digestive tracts, and the kidney. NDEA is also carcinogenic following administration prenatally and in single doses. Dose-response relationships were established in several studies. A metabolite, N-nitroso-N-ethyl-N-(2-hydroxyethyl)amine, produces mainly liver tumors after po administration to rats. NDEA was found to be mutagenic in several types of assays. The general population may be exposed to low levels of NDEA; however, no exposed group suitable for an epidemiological investigation has been identified. No human data are available. Because of the evidence of its carcinogenicity in many animal species, NDEA should be regarded as if it were carcinogenic to humans. (203 refs.)

78-4823 **N-Nitrosodiethanolamine.** (Eng) IARC Working Group (Lyon, France). *In: Some N-Nitroso Compounds.* Magee, P. N., Chairman (International Agency for Research on Cancer: Switzerland): IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 17, 365 pp.; 77-82; 1978.

Chemical and physical data; production, use, occurrence, and analysis; and biological data relevant to the evaluation of carcinogenic risk to humans are presented for N-nitrosodiethanolamine (NDELA). This compound is found in tobacco, pesticides, cosmetics, and, in much higher concentrations (0.02%-3%), in cutting fluids. NDELA is carcinogenic in BD rats after po administration (600-1,000 mg/kg/day, total dose 150-300 g/kg) and in Syrian golden hamsters after sc injection (2,260 mg/kg 2x/wk x 7 or 565 mg/kg x 27 over 45 wk; total doses approx 41 g/kg). It produces hepatocellular carcinomas and renal adenomas in the rats and adenocarcinomas of the nasal cavity, papillary tumors of the trachea, hepatocellular adenomas, and local fibrosarcomas in the hamsters. Although no case reports or epidemiological data for humans are available, the experimental data indicate that NDELA should be regarded as if it were carcinogenic to humans. (11 refs.)

78-4824 **N-Nitrosodi-N-Propylamine.** (Eng) IARC Working Group (Lyon, France). *In: Some N-Nitroso Compounds.* Magee, P. N., Chairman (International Agency for Research on Cancer: Switzerland): IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 17, 365 pp.; 177-189; 1978.

Chemical and physical data and the results of carcinogenicity

and related studies are given for N-nitrosodi-n-propylamine (NDPA), a compound that has been found in the wastewater from 3/28 chemical plants, cheese, alcoholic beverages, and in two pesticides [Treflan (trifluralin) and isopropalin]. NDPA is carcinogenic in rats after po administration and in rats and hamsters after sc injection, producing benign and malignant tumors of the liver, kidney, esophagus, and respiratory tract. The metabolite N-nitroso-N-(2-hydroxy-n-propyl)-n-propylamine produces benign and malignant tumors of the respiratory tract and liver upon sc injection into rats and hamsters. NDPA was mutagenic in *Salmonella typhimurium*, *Escherichia coli*, and Chinese hamster V79 cells. The general population may be exposed sporadically to low levels of NDPA, but there are not human data available. Reports of relatively high levels in Treflan (154,000 and 190,000 μg/liter) may permit the identification of exposed groups. These is sufficient evidence of a carcinogenic effect of NDPA in two animal species; therefore, the compound should be regarded as if it were carcinogenic to humans. (47 refs.)

78-4825 **N-Nitrosodi-N-butylamine.** (Eng) IARC Working Group (Lyon, France). *In: Some N-Nitroso Compounds.* Magee, P. N., Chairman (International Agency for Research on Cancer: Switzerland): IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 17, 365 pp.; 51-75; 1978.

The carcinogenic risk of N-nitrosodi-n-butylamine (NDBA) to humans was evaluated by reviewing the current data. NDBA has no known commercial uses. It has been found in tobacco smoke, in the effluent from a coke plant, in food (soybean oil, cheese, various pork products, canned and powdered soups, and canned meals), experimental animal feed, and in a commercial corrosion-resistant film. NDBA is carcinogenic in all animal species tested (mice, rats, rabbits, guinea pigs, and Syrian golden, Chinese, and European hamsters) by the po, sc, ip, or iv routes. It produces leukemia and benign malignant tumors in the urinary bladder, esophagus, liver, respiratory tract, stomach, and intestine; it is particularly effective as a bladder carcinogen. Administration prenatally and in single doses also results in malignancy. The two metabolites, N-nitroso-n-butyl-N-(4-hydroxybutyl)amine and N-nitroso-n-butyl-N-(3-carboxypropyl)amine, are also carcinogenic, the first in mice, rats, hamsters, and dogs and the second in rats. NDBA was found to be mutagenic in several types of assays. The general population may be exposed sporadically to low levels of NDBA, but no human data on its carcinogenicity are available. However, the animal data suggest that NDBA should be regarded as if it were carcinogenic in humans. (93 refs.)

78-4826 **N-Nitroso-N-methylurea.** (Eng) IARC Working Group (Lyon, France). *In: Some N-Nitroso Compounds.* Magee, P. N., Chairman (International Agency for Research on Cancer: Switzerland): IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 17, 365 pp.; 227-255; 1978.

Biological data on the carcinogenicity of N-nitroso-N-methylurea (NMU) were evaluated relative to the carcinogenic risk to humans. NMU has been studied for use as a cancer chemotherapy agent and for its mutagenic effects on various plants. NMU is carcinogenic in mice, rats, guinea pigs, rabbits, gerbils, pigs, dogs, monkeys and Syrian golden, Chinese, and European hamsters. It induces benign and malignant tumors following administration by most routes, including ingestion. Tumor induction occurs in the nervous tissue, stomach, esophagus, pancreas, respiratory tract, intestine, lymphoreticular tissues, skin, and kidney. It is carcinogenic following administration prenatally and in single doses. The mutagenicity of NMU has been demonstrated in various systems. There is sufficient evidence of a carcinogenic effect of NMU in several animal species. Although no human data were available, NMU should be regarded as if it were carcinogenic to humans. (122 refs)

78-4827 **Nervous-system-specific Carcinogenesis by Ethylnitrosourea in the Rat: Molecular and Cellular Aspects.** (Eng) Rajewsky, M. F. (Memorial Sloan-Kettering Cancer Center, New York, NY, 10021); Augenlicht, L. H.; Biessmann, H.; Goth, R.; Hulser, D. F.; Laerum, O. D.; Lomakina, L. Y. *In: Mechanisms of Carcinogenesis. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book B), 699 pp.; 709-728; 1977.

Molecular and cellular aspects of the induction of nervous system (NS) tumors in the rat by ethylnitrosourea (ENU) are reviewed. The extranuclear oxygen-6 atom of guanine in the DNA is a major site of ethylation by ENU, and O^6-ethylation of guanine in DNA is not restricted to a situation in which the extranuclear oxygen atom is unprotected by hydrogen bonding (ie, replicating DNA). Selective persistence of O^6-methylguanine in rat brain DNA was also demonstrated after application of the predominantly NS-specific carcinogen methylnitrosourea. Dissociated fetal rat brain cells (FBC) treated transplacentally with ENU became tumorigenic after 200 days. This time interval is of the same order as the median time until death with neuroectodermal tumors in the offspring of rats injected with the same dose of ENU at the same stage of gestation. Solid, transplantable tumors developed upon sc reimplantation of the cultured tumor cells. These tumors appeared histologically as neurinoma-, glioma-, or glioblastomalike and frequently pleiomorphic neoplasms. Although subpopulations of probable high-risk FBC have not been defined, proliferative glial precursors are potential candidates. (71 refs.)

78-4828 **Animal Toxicology.** (Eng) Kimbrough, R. (Toxicology Branch, Clinical Chemistry Div., Bureau Labs., Center Disease Control, Dept. Health, Education and Welfare, Public Health Service, Atlanta, GA, 30333); Buckley, J.; Fishbein, L.; Flamm, G.; Kasza, L.; Marcus, W.; Shibko, S.; Teske, R. *Environ Health Perspect* 24: 173-185; 1978.

Recently published information on the toxic effects of polychlorinated biphenyls (PCB) in mammals and the results of experimental studies in birds are reviewed. Specific topics include the acute toxicity of PCB and polybrominated biphenyls (PBB); the subacute and reproductive effects of PCB, PBB, and chlorinated dibenzofurans; and the mutagenicity and teratogenicity of PCB and PBB. Hepatomas and hyperplastic nodules were produced in the livers of BALB c/J mice fed Aroclor 1254 (300 ppm), hepatocellular carcinomas and nodular hyperplasia in male dd mice fed Kanechlor 500, (100-500 ppm), liver tumors in mice fed 250 ppm α-hexachlorocyclohexane (α-HCH) or in mice fed 250 ppm PCB and 100 or 50 ppm α-HCH or 250 or 100 ppm β-HCH, and liver tumors in rats fed Aroclor 1260, Kanechlor 400, and Aroclor 1254. The induction of liver tumors in Sprague-Dawley rats by known carcinogens such as 3′-methyl-4-dimethylaminoazobenzene, N-2-fluorenylacetamide, and diethylnitrosamine was inhibited by Kanechlor 500. PCB have also been implicated as immunosuppressants. The degree of toxicity of chlorinated naphthalenes increases with the degree of chlorination; the higher chlorinated naphthalenes have been associated with chloracne and liver damage in humans. (96 refs.)

78-4829 **Carcinogenic Potential of the Polychlorinated Biphenyls.** (Eng) Allen, J. R. (Dept. Pathology, Univ. Wisconsin Medical Sch., Madison, WI, 53706); Norback, D. H. *In: Incidence of Cancer in Humans. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4, 602 pp.; 173-186; 1977.

The general toxic effects and carcinogenic action of polychlorinated biphenyls (PCBs') are reviewed. Marked hypertrophy of the liver and stimulation of the mixed-function oxidases of the liver occur in experimental animals exposed to PCB's, and hypertrophic, hyperplastic, dysplastic, metaplastic, and carcinogenic changes have been recorded in chronically exposed rodents. Chronic feeding studies in rats and mice suggest that the more highly chlorinated PCB congeners, which are more slowly metabolized and persist in the tissues indefinitely, are the likely precarcinogens. Biochemical data also suggest that PCB's might be carcinogenic. However, only preliminary observations have been made on the association of PCB exposure and tumor development in humans. Until the potential danger of low-level, long-term exposure of the human population to PCB's is better understood, it must be assumed that any level of exposure may be injurious to human health. (51 refs.)

78-4830 **Metabolism of Chlorinated Alkenes and Alkanes as Related to Toxicity.** (Eng) Henschler, D. (Institut fur Pharmakologie und Toxikologie, Univ. Wurzburg, D-87 Wurzburg, W. Germany). *J Environ Pathol Toxicol* 1(2): 125-133; 1977.

Chlorine substitution in aliphatic compounds results in a destabilization in alkanes and a stabilization in alkenes. With alkanes, therefore, the main pathways of metabolic transformation to reactive intermediates are radical formation by a C-C break and dechlorination or dehydrochlorination. In the chlorinated ethylenes, the first metabolic transformation step is oxidation to electrophilic oxiranes. These compounds may be hydrolized enzymatically or nonenzymatically, react with cellular nucleophiles, or rearrange to either chlorinated aldehydes or acyl chlorides. With tetrachloroethylene, 1,2-cis-dichloroethylene, trans-dichloroethylene, 1,1-dichloroethylene, and vinyl chloride, the metabolites identified in in vivo experiments are identical to the thermal rearrangement products of the respective oxiranes. An exception is trichloroethylene, whose thermal rearrangement product is dichloroacetyl chloride; its metabolites in vivo, however, are entirely derived from trichloroacetaldehyde. Mutagenic and carcinogenic activities in the chlorinated ethylenes are determined by the stability of their oxiranes. This stability is higher in symmetrical than in asymmetrical chlorine substitution compounds: the relatively unstable and asymmetric oxiranes of trichloroethylene, 1,1-dichloroethylene, and vinyl chloride are mutagenic in the Ames test, but the more stable asymmetric oxiranes of tetra-, 1,2-cis-, and trans-dichloroethylenes are inactive. (20 refs)

78-4831 **Recent Findings on the Carcinogenicity of Chlorinated Olefins.** (Eng) Maltoni, C. (Inst. Oncology and Tumor Center, Bologna, Italy). *Environ Health Perspect* 21: 1-5; 1977.

Major factors affecting the carcinogenicity of vinyl chloride (VC) and vinylidene chloride (VDC) are discussed. Although the two compounds have very similar molecular structures, they have widely different biological effects. VS is a multipotential carcinogen, but VDC has produced tumors only in the murine kidney. Dose, concentration, length of treatment, route of administration, and animal species, strain, sex, and age also significantly affect the neoplastic response. These factors may alter the metabolic pathway of the test compounds. The carcinogenicity of VC and VDC is due to their active metabolites, probably epoxy derivatives. Animal species, strain, and sex greatly affect the production of active metabolites of VDC. In Swiss mice and Sprague-Dawley rats, there is a parallelism between the toxic and carcinogenic effects of VDC in relation to species and sex. Confirmation of

his parallelism in other strains would indicate new routes for stablishing experimental animal models, and for understanding the mechanisms of action of many organic carcinogens. (5 refs)

78-4832 **Vinyl Chloride: A Case for the Use of Laboratory Bioassay in the Regulatory Control Procedure.** (Eng) Wagoner, J. K. (Industry-wide Studies Branch, Div. Surveillance, Hazards Evaluations and Field Studies, Natl. Inst. Occupational Safety and Health, Cincinnati, OH, 45202); Infante, P. F. *In: Human Risk Assessment. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book C), 583 pp.; 1797-1805; 1977.

The need for laboratory bioassays in the regulatory control of chemicals is illustrated using vinyl chloride (VC) as an example. The induction of skin, lung, and bone tumors in rats exposed by inhalation to high VC levels (levels not infrequently approached in the industrial setting) was first reported in 1971, 40 yr after VC's commercial introduction but 3 yr before three cases of liver angiosarcoma were reported among workers at a VC polymerization facility. A follow-up study, initiated as a result of these initial angiosarcoma cases, showed a significant excess of deaths from malignant neoplasms among VC workers, compared with US white male death rates. Excess cancer mortality was found for four organ systems: brain and CNS, respiratory system, hepatic system, and lymphatic and hematopoietic system. The cancer risk increased with increasing years of exposure. In the follow-up study, 11/14 confirmed cases of biliary or liver cancer were hepatic angiosarcoma. Among 8 bronchogenic carcinomas, 5 were large-cell undifferentiated and 3 were adenocarcinomas, which is not consistent with distributions previously reported for inhaled carcinogens. A recent bioassay was predictive not only for the carcinogenicity of VC but also for several of the target organs. VC is mutagenic in microbial test systems, and VC metabolites have induced mutations in mammalian cells. Wives of VC-exposed men have a significantly high risk of fetal loss. Thus, both mutagenic and carcinogenic assays predicted the potential hazards of VC. (34 refs.)

78-4833 **Pharmacokinetics of Vinyl Chloride.** (Eng) Bolt, H. M. (Inst. Toxicology, Univ. Tubingen, Wilhelmstrasse 56, D-7400 Tubingen 1, W. Germany). *Gen Pharmacol* 9(2): 91-95; 1978.

Data on the pharmacokinetic behavior of vinyl chloride (VC), all of which have been obtained from studies with rats, are reviewed. Consistent evidence shows that, above a saturation concentration, which on inhalation exposure is reached at 250 ppm VC, nonlinear (dose-dependent) pharmacokinetics apply. Two different models describing the pharmacokinetics of VC have been published. They show that VC can leave the body very rapidly via expiration by the lungs. However, special conditions apply if rats are exposed to atmospheric VC: the compound equilibrates with the organism within 15-30 min and is removed from this equilibrium metabolically, probably by formation of the reactive epoxide. The rapid elimination of VC and its major metabolites from the organism agrees with the current theory that a reactive, short-lived metabolite, which occurs in low concentrations only, may be responsible for the toxic effects of VC. (25 refs)

78-4834 **Chloroprene: Observations of Carcinogenesis of Mutagenesis.** (Eng) Infante, P. F. (Industry-wide Studies Branch, Div. Surveillance, Hazard Evaluation and Field Studies, Natl. Inst. Occupational Safety and Health, Cincinnati, OH, 45202); Wagoner, J. K.; Young, R. J. *In: Incidence of Cancer in Humans. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4, 602 pp.; 205-217; 1977.

Observations of excessive lung and skin cancer associated with chloroprene production were reported in the Russian literature in 1972. However, it was not until 1974, when an epidemic of liver, brain, and lung cancer among vinyl chloride (VC) polymerization workers was identified, was attention in the US focused on the carcinogenic potential of chloroprene. Chloroprene is mutagenic in bacteria, causes recessive lethality in *Drosophila*, causes dominant lethality and chromosome aberrations in rat bone marrow cells, and has been associated with sterility in mice and rats. A significant excess of chromosome aberrations and a reduction in the numbers and motility of sperm have been reported in chloroprene workers, and a threefold excess of miscarriages has been reported among their wives. In the absence of adequate data, a final evaluation of the carcinogenicity of chloroprene cannot be made. However, given its other effects, the possible carcinogenicity of chloroprene may be only of academic interest from a public health point of view. The data for VC and chloroprene may serve as the basis for a more aggressive role by genetic toxicologists in the assay of industrial chemicals. (35 refs.)

78-4835 **Pulmonary Fibrosis and Lung Cancer Caused by Exposure to Pesticides.** (Ger) Barthel, E. (Sitzungsberichte der Akademie der Wissenschaften der DDR, Berlin, E. Germany). *Akademie der Wissenschaften* (2): 33-45; 1978.

Experimental, clinical, and epidemiological data on the association between exposure to pesticides, especially that of

farm workers, and the development of pulmonary fibrosis and lung cancer are reviewed. (48 refs)

78-4836 **Underestimation of Chronic Toxicities of Food Additives and Chemicals: The Bias of a Phantom Rule.** (Eng) Kon, S. H. (Henry Dazian Dept. Chemistry, Mount Sinai Hosp., New York, NY, 10029). *Med Hypotheses* 4: 324-339; 1978.

Although it has been assumed that dose-response curves of toxic compounds must never reverse, a literature review of the curves for several food additives revealed toxicity peaks at low doses,often at the lowest dose tested. Similar relationships of max effect at low doses abound in nature. It is suggested that compounds regulated solely on the basis of a progressive dose-response curve may constitute a public health hazard. (71 refs.)

78-4837 **Nontoxicity of Mold Cultures Used in Cheese Making.** (Ger) Sieber, R. (Forschungsanstalt fur Milchwirtschaft, CH-3097 Liebefeld-Bern, Switzerland). *Z Ernaehrungswiss* 17(2): 112-123; 1978.

The only carcinogenic mycotoxin discovered in cheese to date has been aflatoxin M_1, which may have originated from the use of contaminated milk. Although feeding pure *Penicillium camemberti var. candidum* culture to animals produced tumors attributable to mycotoxins, further studies with various mold culture strains have not confirmed these findings. It is concluded that the use of mold cultures for cheese making does not involve human health risks. (55 refs.)

78-4838 **Review of Methods for the Determination of Aflatoxin B, G, and M in Foodstuffs and Feed.** (Ger) Luthy, J. (Institut fur Toxikologie der Eidgenossischen Technischen Hochschule, Universitat Zurich, Schorenstrasse 16, CH-8603 Schwerzenbach, Switzerland). *Mitt Geb Lebensmittelunters Hyg* 69(2): 200-219; 1978.

The most important methods for analyzing aflatoxin B, G, and M in foodstuffs and feed are reviewed. The topics discussed include the physical-chemical properties of aflatoxins, the analytical methods, collaborative studies with these methods, the identification and analysis of aflatoxin M, and the application of new methods, high-pressure liquid chromatography and radioimmunoassay, for aflatoxin detection. (106 refs.)

78-4839 **Field Studies on Liver Cell Cancer.** (Eng) Linsell, C. A. (International Agency Res. Cancer, 69008 Lyon, France); Peers, F. G. *In: Incidence of Cancer in Humans. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4, 602 pp.; 549-556; 1977.

Field studies relating human exposure to aflatoxins and viral hepatitis to an increased risk of liver cell cancer are reviewed. Studies in several African countries and Thailand showed a correlation between aflatoxins in ground nuts, market food samples, and foods ready for ingestion and increased liver cell cancer. The major problem in all these studies was the registration of cancer patients, which made interpretation of the data difficult. The studies suggest a possible dose-response relationship and justify seeking more definitive proof by an intervention program. Hepatitis B has also been suggested as an etiologic agent for liver cancer, the carrier state definitely being associated with this. There is a preponderance of liver cancer in men. It is possible that men metabolize the ultimate carcinogen of aflatoxin less well than women and that men are more susceptible than women to the acute toxicity and chronic carcinogenic effect of aflatoxin. Hepatitis B affects more men than women and the carrier state is more common in men. Liver cancer appears to be an excellent model for study of the interaction between two well-defined factors, one chemical and the other viral. (26 refs.)

78-4840 **Mode of Action and Human Health Aspects of Aflatoxin Carcinogenesis.** (Eng) Butler, W. H. (Dept. Histopathology, Saint George's Hosp. Medical Sch., Blackshaw Road, London SW17 OQT, England); Neal, G. E. *Ann Nutr Aliment* 31(4/5/6): 949-956; 1978.

Studies of the mode of action of aflatoxin (AF) carcinogenesis are reviewed. A high incidence of hepatic carcinoma is induced in rats by feeding them 5 ppm AF for 6 wk followed by return to a normal diet. At the end of the 6-wk treatment period, the liver contains multiple foci of cells that are characterized by the presence of starvation-resistant glycogen and a loss of glucose-6-phosphatase activity. These findings are similar to those reported in nitrosamine carcinogenesis. However, the foci in livers of rats fed AF are present throughout the liver, and it is difficult to determine which, if any, of them are related to the final neoplasm or the fate of those that do not develop into carcinoma. If the estimated daily dietary intake of AF is given to rats as a single ip injection, there is a marked inhibition of both RNA and DNA synthesis, with the inhibition of DNA synthesis being considerably greater than that of RNA. This parallels the changes observed during the early stages of the 6-wk feeding cycle. In all studies of experimental hepatocarcinogenesis using AF as the inducing agent, it is apparent that the neoplasm usually arises in a liver that is free of cirrhosis. The experience in humans is that in Europe and North America, most hepatocarcinomas arise in cirrhotic patients. However, in areas where hepatocarcinoma

is a relatively common disease, many such tumors arise in livers showing no cirrhosis. It is possible that in areas with a high incidence of hepatic neoplasia, multiple factors influence the development of the carcinoma. It has been shown, for example, that animals fed low-lipotrope diets have an increased susceptibility to hepatocarcinomas. (23 refs)

78-4841 **Occupational and Environmental Standards for Asbestos and Their Relation to Human Disease.** (Eng) Nicholson, W. J. (Mount Sinai Sch. Medicine, City Univ. New York, New York, NY, 10029). *In: Human Risk Assessment. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book C), 583 pp.; 1785-1796; 1977.

The effectiveness of occupational and environmental asbestos standards is considered. The current occupational standard for asbestos is a time-weighted av exposure limit of 2 fibers/ml. Additional provisions for controlling exposures based on work practices are included in this standard, but they are mandatory only if the asbestos air concentration exceeds the established value. Extrapolation from studies on the relationship between lung cancer and exposure of workers in asbestos plants indicates that a continuous 20-yr fiber exposure of 0.4 (less than the proposed Department of Labor standard of 0.5 fibers/ml) could cause a fourfold increase in lung cancer. The ambient-air standard for asbestos simply states that there can be no visible emissions from any facility producing or using asbestos materials. Exposure of the general population occurs from the fireproofing of office buildings by spraying with material containing up to 15% asbestos, a practice no longer permitted. However, the demoliton of such buildings, the erosion of fibers from previously applied asbestos, and damage to asbestos during repair work pose serious exposure problems now and in the future. No standards exist for asbestos levels in water supplies, which range from <0.1 to >200 μg/liter. Although no direct epidemiologic evidence links ingestion of asbestos to gastrointestinal cancer, an excess of such tumors has been found among asbestos workers. There are also no appropriate standards for the use and disposal of mining and quarrying material contaminated with asbestos fiber or for the use of asbestos in consumer products. (17 refs.)

78-4842 **Cancer Risk of Asbestos Exposure.** (Eng) Selikoff, I. J. (Evnironmental Sciences Lab., Mount Sinai Sch. Medicine, City Univ. New York, New York, NY, 10029). *In: Human Risk Assessment. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book C), 583 pp., 1765-1784; 1977.

The association between asbestos exposure and cancer is reviewed, and the scope of the problem is considered. Asbestos has been confirmed as a cause of asbestosis, lung cancer, pleural and peritoneal mesothelioma, and gastrointestinal cancer; it may also be related to cancer of the buccal cavity, pharynx, and larynx. Approx 1/5 asbestos workers who were exposed under conditions that existed in the past die of lung cancer. Peritoneal mesotheliomas occur more often than pleural mesotheliomas in asbestos workers, but pleural mesotheliomas are more common in cases of environmental, family contact, or neighborhood exposures. The long clinical latency period in asbestos-related disease has made it difficult to evaluate the quantitative relationship between the amount of exposure and the subsequent risk. However, there appears to be a dose-disease-response gradient for asbestos, with disease much more likely to occur as a result of heavier exposure. Based on studies of the time of death from lung cancer and pleural and peritoneal mesotheliomas in relation to the elapsed time from onset of first exposure, serious risk begins $>$ 20 yr after onset of first exposure. Cigarette smoking increases the risk of lung cancer in asbestos workers, but it is not associated with pleural nor peritoneal mesothelioma. Cigarette-smoking asbestos workers are also at risk for esophageal cancer but not gastrointestinal cancer. From the public health perspective, low-level environmental exposure and end-product contamination are more widespread problems than occupational exposure. (45 refs)

78-4843 **Possible Effects of Drugs on the Occurrence of Malignant Neoplasms.** (Cro) Cicek, J. (Nazorova 37a, 41000 Zagreb, Yugoslavia). *Libri Oncol* 6(3/4): 37-45; 1977.

Radioisotopes, antilymphocyte serum, antimetabolites, chloronaphazine, melphalan, cyclophosphamide, synthetic estrogens, androgens, arsenic compounds, phenacetin, tar-base ointments, and, possibly, diphenylhydantoin, chloramphenicol, amphetamine, and reserpine are cancer-causing drugs in humans. (59 refs)

78-4844 **Metronidazole, Isoniazid, and the Threat of Human Cancer.** (Eng) Goldman, P. (Clinical Pharmacology Div., Dept. Pharmacology, Harvard Medical Sch., Boston, MA, 02115); Ingelfinger, J. A.; Friedman, P. A. *In: Incidence of Cancer in Humans. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4, 602 pp.; 465-474; 1977.

The benefits and cancer-causing potentials of metronidazole, an antibiotic drug used to treat trichomonal vaginitis, are

discussed. The effectiveness of the drug depends on the dose given, the dose currently approved by the Food and Drug Administration being 250 mg tid for 10 days. This dose, or even a dose of 250 mg tid for 7 days, may be unnecessarily high, since total doses as low as 2 g have been successful. There have been no direct estimates of human cancer risk associated with metronidazole ingestion, but the drug causes an increased incidence of pulmonary adenomas in mice. Metronidazole also has chemical and biological properties that are often associated with known carcinogens. On the basis of the laboratory evidence, there is no reason to suspect that metronidazole is a more potent carcinogen than isoniazid. The latter has been tested directly in humans and has not been associated with a large increase in cancer within the 15 yr following treatment. However, in the absence of a reliable method for extrapolating from laboratory data to human risk, it would be unwise to conclude that metronidazole is no more risky than isoniazid. Thus, metronidazole should be given only in the necessary dose to patients with symptomatic trichomonal vaginitis. (32 refs)

78-4845 **Hycanthone and Other Antischistosomal Drugs: Lack of Obligatory Association Between Chemotherapeutic Effects and Mutagenic Activity.** (Eng) Bueding, E. (Dept. Pathobiology, Sch. Hygiene and Public Health, Johns Hopkins Univ., Baltimore, MD, 21205); Batzinger, R. P. *In: Incidence of Cancer in Humans. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4, 602 pp.; 445-463; 1977.

The association between the schistosomicidal and mutagenic activities of antischistosomal drugs is discussed. Hycanthone (HCT) is a potent mutagen for bacteria, yeast, and mammalian cells and it is carcinogenic in mice, particularly in those infected with *Schistosoma mansoni.* The nitroheterocyclic schistosomicide niridazole is also mutagenic and carcinogenic, and the mutagenic activity of furapromidium is of the same order of magnitude as that of niridazole (its carcinogenicity has not been tested). The mutagenic activities of two other drugs, metrifonate and oxamniquine, are several orders of magnitude lower than that of HCT. The antischistosomal potencies of HCT and of a chloroindazole analog of HCT are equal, but the mutagenic and carcinogenic potencies of the analog are much lower. N-oxidation of the analog results in the potent schistosomicide IA-4 N-oxide, whose mutagenic potency is even weaker and whose LD_{50} is 12 times higher than that of HCT. A new antischistosomal compound, 4-isothiocyanato-4′-nitrodiphenylamine, is mutagenic in host-mediated assays, but if it is given after the host's intestinal bacterial flora has been reduced by antibacterial agents, it is nonmutagenic. Thus, schistosomicidal and mutagenic activities can be completely dissociated from each other. (83 refs)

78-4846 **Schistosomiasis and Neoplasia.** (Eng) Cheever, A. W. (Lab. Parasitic Diseases, Natl. Inst. Allergy and Infectious Diseases, NIH, Public Health Service, U.S. Dept. Health, Education, and Welfare, Bethesda, MD, 20014). *J Natl Cancer Inst* 61(1): 13-18; 1978.

The association between schistosomiasis and cancer of the urinary bladder, hepatocellular carcinoma, lymphoma and leukemia, and carcinoma of the colon is considered. Rigorous statistical proof of the association between *Schistosoma haematobium* infection and bladder cancer has not been obtained, but most published data tend to confirm the association. Etiologic factors in schistosomal bladder cancer may be chronic inflammation of the bladder and urinary retention, carcinogenic substances in the schistosome in the schistosome eggs, effects of schistosome infection on the immune system, the interaction of bacteria in the urine with excreted substances, and the strain of schistosome. Hepatomas were equally frequent in uninfected and schistosome-infected patients in autopsy series from several countries. In Japan, both hepatoma and circulating hepatitis B surface antigen were significantly more frequent in autopsied patients with *S. japonicum* than in those without, but most autopsied patients with schistosomiasis and hepatoma also had posthepatitis cirrhosis. Equivocal increases in the frequency of hepatoma have been reported in animals infected with *S. mansoni.* An association between giant follicular lymphoma of the spleen and hepatosplenic schistosomiasis was found in Brazil. Several autopsy series suggest an association of either lymphoma, leukemia, or both with schistosomiasis. Cancers of the colon, ovaries, uterus, and other organs have been attributed to schistosomiasis, but no evidence of more than a coincidental association has been provided. (81 refs)

78-4847 **Carcinogenic Hazards of Organic Chemicals in Drinking Water.** (Eng) Harris, R. H. (Environmental Defense Fund, Washington, DC, 20036); Page, T.; Reiches, N. A. *In: Incidence of Cancer in Humans. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4, 602 pp.; 309-330; 1977.

Studies dealing with elevated cancer mortality rates resulting from the presence of carcinogens in the drinking water are reviewed. Five main topics are discussed: (1) organic carcinogens in drinking water, (2) approaches to assessing the potential health consequences of these chemicals, (3) recent epidemiologic studies, (4) statistical problems in relating exposure to water pollutants to cancer mortality, and (5) the application of the results of these epidemiologic studies to assessment of the risk of low-level carcinogenic exposure. Studies indicate that although a wide variety of chemical carcinogens are present in the drinking water, their concentrations are low. However, epidemiologic studies in Louisiana,

hio, and New Jersey support the hypothesis that carcinoens in drinking water are related to human cancer. Since ese findings reflect exposure to carcinogen levels present)-30 yr ago and present-day levels are assumed to be higher, ore noticeable effects may be expected in the future. (38 fs.)

8-4848 **Potentially Carcinogenic Species Emitted to the Atmosphere by Fossil-fueled Power Plants.** Eng) Natusch, D. F. (Dept. Chemistry, Colorado State Iniv., Fort Collins, CO, 80523). *Environ Health Perspect* 22: 9-90; 1978.

The identities and physicochemical characteristics of potenial carcinogens emitted by fossil-fueled power plants are preented. Many carcinogens are preferentially concentrated on he surface of respirable fly ash particles, enabling them to ome in contact with lung tissue when inhaled. There is little nformation on the identities of particulate polycyclic organic ompounds emitted from the plants. The chemical changes hat these compounds may undergo following emission but efore inhalation are important in determining their potential arcinogenicity. (34 refs)

78-4849 **Trends in Urban Air Pollution in the United Kingdom in Relation to Lung Cancer Mortality.** (Eng) Lawther, P. J. (MRC Environmental Hazards Unit, St. Bartholomew's Hosp. Medical Coll., Charterhouse Square, London EC1M 6BQ, England); Waller, R. E. *Environ Health Perspect* 22: 71-73; 1978.

The possible role of atmospheric carcinogens in lung cancer is considered in view of the substantial reduction in air pollution, particularly in components such as benzo(a)pyrene (BP), in urban areas of the United Kingdom during the past few decades. Although overall trends in lung cancer mortality have been influenced largely by changes in smoking habits since the late 1930's, the marked contrasts that once existed between lung cancer death rates in urban and rural areas have gradually diminished. Thus, air pollution may have contributed to the urban-rural differences in lung cancer before the Clean Air Act of 1956. In London, BP concentrations are now one-tenth of those in the period 1949-1951. (5 refs)

78-4850 **Are Chemicals the Main Cause of Cancer? Fateful Change Processes in the Body--Mainz Scientists Examine the Role of Benzpyrene from Waste Gases and Smoke.** (Eng) Zimmermann, D. (No affiliation given). *Dtsch Forschung* 17(4): 1-3; 1978.

Studies of the carcinogenicity of benzo(a)pyrene (BP) suggest that the compound is fat-soluble and, therefore, accumulates in the body where it is transformed by certain enzymes into a highly reactive epoxide that can disrupt cellular processes and bind to nucleic acids. It is possible that an antienzyme, which can prevent the formation of this epoxide, may be able to suppress the carcinogenicity of BP. (no refs.)

78-4851 **Some Recent Findings Concerning Cigarette Smoking.** (Eng) Hammond, E. C. (Dept. Epidemiology and Statistical Res., American Cancer Society, New York, NY, 10017); Garfinkel, L.; Seidman, H.; Lew, E. A. *In: Incidence of Cancer in Humans. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4, 602 pp.; 101-112; 1977.

Some recent findings concerning the effects of cigarette smoking are discussed. Death rates are higher in smokers than in nonsmokers and they increase with the number of cigarettes smoked per day and with the number of years spent smoking. A prospective study of > 1,000,000 subjects was carried out between 1959 and 1965, and the 897,825 subjects who were still alive in 1965 were studied until 1971 or 1972. For both men and women for both study periods, the adjusted number of deaths and the adjusted number of deaths from lung cancer were lowest among smokers of low tar and nicotine (T/N) cigarettes and highest among high T/N smokers. The adjusted number of lung cancer deaths was greater in subjects who smoked 20-39 low T/N cigarettes/day than in subjects who smoked 1-19 high T/N cigarettes/day. The overall death rate and the lung cancer death rate were far higher in subjects who smoked low T/N cigarettes than in subjects who never smoked regularly. Thus, reduction of the T/N content of cigarette smoke did not make cigarette smoking safe, although switching from high T/N to low T/N cigarettes would appear to be a small step in the right direction. (7 refs)

78-4852 **The Genetic Expression of Aryl Hydrocarbon Hydroxylase Activity: Evidence for a Receptor Mutation in Nonresponsive Mice.** (Eng) Poland, A. (Dept. Pharmacology and Toxicology, Univ. Rochester Sch. Medicine and Denistry, Univ. Rochester, Rochester, NY, 14642); Kende, A. *In: Mechanisms of Carcinogenesis. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book B), 699 pp.; 847-867; 1977.

The nature of the aryl hydrocarbon (*Ah*) locus in the mouse was determined. Previous studies have shown that the *Ah* locus determines the expression of aryl hydrocarbon hydroxylase (AHH) activity and cytochrome P_1-450; they also implicate the *Ah* locus in mediating the mutagenesis and car-

cinogenesis produced by certain polycyclic aromatic hydrocarbons (PAH). 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) was used to determine the nature of the *Ah* locus and how PAH stimulate AHH activity. TCDD was a potent inducer of hepatic AHH activity and cytochrome P_1-450 in rats and in nonresponsive mice, which were not responsive to the inductive activity of 3-methylcholanthrene. Experimental evidence indicates that the hepatic cytosol from C57BL/6J mice contains a binding species with a high affinity for TCDD, that the binding properties of this cytosol species correspond extremely well to the properties predicted for the induction receptor, and that the mutation in nonresponsive strains of mice appears to result in a receptor with a diminished affinity for inducing ligands. It is postulated that the *Ah* locus codes for the cytosol binding protein, which serves as a cellular recognition site for PAH, TCDD, and similar compounds, and that the binding of these inducers to the receptor in some manner serves as a master switch to initiate the expression of numerous noncontiguous structural genes. (43 refs.)

78-4853 **Aryl Hydrocarbon Hydroxylase and Bronchogenic Carcinomas Associated with Smoking (Letter to Editor).** (Eng) Korsgaard, R. (Res. Dept. I, Univ. Hosp., Wallenberg Lab., Univ. Lund, S-220 07 Lund, Sweden); Trell, E. *Lancet* 1(8073): 1103-1104; 1978.

Studies have confirmed the finding that aryl hydrocarbon hydroxylase (AHH) is the major activator of polycyclic aromatic hydrocarbon carcinogens in patients with squamous cell carcinoma of the lung. Variations in the assessment of AHH inducibility can be minimized by using T- and B-cell mitogens, equal numbers of stimulated lymphocytes for test and control studies, and by excluding any enzyme-inducing capacity from the media. (10 refs)

78-4854 **Properties of the Liver Microsomal Monooxygenase System and Epoxide Hydrase: Factors Influencing the Metabolism and Mutagenicity of Benzo[a]pyrene.** (Eng) Levin, W. (Dept. Biochemistry and Drug Metabolism, Hoffman-La Roche, Inc., Nutley, NJ, 07110); Lu, A. Y.; Ryan, D.; Wood, A. W.; Kapitulnik, J.; West, S.; Huang, M. T.; Conney, A. H.; Thakker, D. R.; Holder, G.; Yagi, H.; Jerina, D. M. *In: Mechanisms of Carcinogenesis. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book B), 699 pp.; 659-682; 1977.

The metabolism of benzo(a)pyrene (BP) by the microsomal monooxygenase systems and epoxide hydrases of animal and human tissue is reviewed. The liver microsomal metabolism of BP varied with different enzyme inducers, animal species, and strains of mice. In addition, the metabolism of BP by lung microsomes from 3-methylcholanthrene-treated mice differed from that by liver microsomes from the same animals. Purified cytochrome P-450 from different animal species treated with different inducers also metabolized BP at significantly different rates. In studies of the metabolism of BP arene oxides by microsomal epoxide hydrase, BP 11,12-oxide differed from the other arene oxides of BP (4,5-, 7,8-, and 9,10-oxides) in being a poor substrate for the enzyme. The dihydrodiols and phenolic metabolites of BP shared arene oxides as common precursors. Epoxide hydrase was shown to participate in both the metabolic activation and detoxification of BP by the monooxygenase system. Data indicated that the human liver contains either a single epoxide hydrase with broad substrate specificity or several epoxide hydrases under similar regulatory control. There were differences between mice and humans in the regulatory systems that control the metabolism of BP, 7-ethoxycoumarin, and 2-acetylaminofluorene. (48 refs.)

78-4855 **Bay-region Epoxides of Dihydrodiols: A Concept Explaining the Mutagenic and Carcinogenic Activity of Benzo[a]pyrene and Benzo[a]anthracene.** (Eng) Jerina, D. M. (Section on Oxidation Mechanisms, Natl. Inst. Arthritis, Metabolism and Digestive Diseases, NIH, Bethesda, MD, 20014); Lehr, R.; Schaefer-Ridder, M.; Yagi, H.; Karle, J. M.; Thakker, D. R.; Wood, A. W.; Lu, A. Y.; Ryan, D.; West, S.; Levin, W.; Conney, A. H. *In: Mechanisms of Carcinogenesis. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book B), 699 pp.; 639-658; 1977.

In order to generalize the concept of diol epoxides as ultimate mutagenic and carcinogenic metabolites, the ability of a reconstituted monooxygenase system containing cytochrome P-448 to activate dihydrodiols of benzo(a)pyrene (BP) and benz(a)anthracene (BA) to mutagenic forms in the presence of a histidine-dependent strain of *Salmonella typhimurium* (TA98) was studied. The results of these studies support the bay-region theory; ie, that bay-region epoxides of dihydrodiols on an angular benzo ring would be good candidates for the ultimate carcinogenic forms of polycyclic aromatic hydrocarbons. The BA 3,4-diol-1,2-epoxides, which contain a bay-region epoxide, were more mutagenic than the other diol epoxides of BA. However, naphthalene, anthracene, and phenanthrene and their trans dihydrodiols could not be activated significantly to mutagens, and the naphthalene 1,2-diol-3,4-epoxides were virtually inactive. Perturbational molecular orbital calculations predict that benzylic carbonium ions at benzylic positions of saturated benzo rings of these small aromatic hydrocarbons are much less easily formed than those from larger hydrocarbons such as BP. The carcinogenicity of BP 7,8-oxide and 7,8-dihydrodiol, the high mutagenicity, upon metabolic activation, of the 7,8-dihy-

odiol compared with other BP derivatives, and the high utagenicity of the 7,8-diol-9,10-epoxides indicate the importance of the bay region for the biological activity of BP. owever, other examples of bay-region epoxides of benzo ng dihydrodiols will have to be examined to establish hether the bay-region theory has general validity. (71 refs.)

3-4856 **The Workplace as a Cause of Cancer--Part I.** (Eng) Schottenfeld, D. (Epidemiology and Preentive Medicine Service, Dept. Medicine, Memorial oan-Kettering Cancer Center, New York, NY); Haas, J. F. *lin Bull* 8(2): 54-60; 1978.

pidemiologic methods used to determine the risks of cancer mong workers exposed to suspect industrial chemicals are eviewed, and a historical overview of occupational carcinoenesis is presented. (38 refs.)

8-4857 **Is There a Health Hazard in Anaesthetic Practice?** (Eng) Spence, A. A. (Dept. Anaesthesia, Vestern Infirmary, Glasgow G11 6NT, Scotland); Knill-Jones, R. P. *Br J Anaesth* 50(7): 713-719; 1978.

A review of health hazards associated with anesthesia practice indicate that women have an increased risk of spontaneous abortion and that both sexes have an increased risk of epatitis, but there is no evidence that operating room workrs are at risk for any other disease. However, it is suggested hat the incidence of cancer, particularly that of leukemia and ymphoma, be monitored in women. (59 refs.)

78-4858 **Trace Concentrations of Anesthetic Gases: A Critical Review of Their Disease Potential.** Eng) Ferstandig, L. L. (Halocarbon Labs., Inc., 82 Burlews Court, Hackensack, NJ, 07601). *Anesth Analg (Cleve)* 57(3): 328-345; 1978.

A review of the histotoxic effects of anesthetics indicates that only high exposure levels produce harmful effects in cells and animals. None of the common halogenated anesthetics produce cancer in animals, and epidemiological studies show no association between exposure and cancer in men and only a dubious association in women. Studies of the effect of anesthetics on reproductive function and disease are inconclusive. (126 refs)

78-4859 **Cosmetic Science--1977.** (Eng) Rieger, M. M. (Warner Lambert Co., Morris Plains, NJ). *Cosmet Toiletries* 93(5): 25-52; 1978.

Progress in surfactant chemistry during 1977 is reviewed along with recent findings on the carcinogenicity of chemicals used in cosmetics. Recent studies have contradicted earlier reports of an association between breast cancer and exposure of hairdressers to hair dyes. Animal studies indicate that neoplasms could result from the intravesicular implantation of foreign bodies alone, suggesting that the results of animal carcinogenicity tests should be subject to careful scrutiny. (190 refs)

78-4860 **Prevention of Epithelial Cancer by Vitamin A and Its Synthetic Analogs (Retinoids).** (Eng) Sporn, M. B. (Lung Cancer Branch, NCI, Bethesda, MD, 20014). *In: Mechanisms of Carcinogenesis. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book B), 699 pp.; 801-807; 1977.

There are two general approaches to the prevention of epithelial cancer: inhibition of initiation and inhibition of progression. The use of vitamin A and its synthetic analogs (collectively called retinoids) in the latter context is discussed. Retinoids have been shown to prevent the development of cancer in the skin, respiratory tract, mammary gland, and urinary bladder of experimental animals. There is an excellent rationale for using these agents to prevent cancer by the enhancement of intrinsic epithelial defense mechanisms. The application of these agents for the prevention of cancer in high-risk human populations is thus worthy of consideration. Future developments in the synthetic chemistry of retinoids should make new structures available that will be even more specific, more potent, and less toxic for practical cancer prevention. (26 refs.)

78-4861 **Kinetics of Tumor Formation and Low Risk Assessment.** (Eng) Scherer, E. (Div. Chemical Carcinogenesis, Antoni Van Leeuwenhoek-Huis, Netherlands Cancer Inst., Amsterdam, Netherlands); Emmelot, P. *In: Carcinogens: Identification and Mechanisms of Action. Proceedings of the Thirty-First Annual Symposium on Fundamental Cancer Research Held at Houston, Texas, 1-3 March 1978.* University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, NCI, American Cancer Society. (Austin, Texas). 22-23 pp.; 1978. (no refs)

78-4862 **The Role of Diet in Human Carcinogenesis with Special Reference to Endometrial Cancer.** (Eng) Armstrong, B. K. (Dept. Medicine, Univ. Western Australia, Nedlands, Western Australia 6009, Australia). *In: Incidence of Cancer in Humans. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4, 602 pp.; 557-565; 1977.

Possible mechanisms for the role of diet in human carcino-

genesis are: (1) ingestion of carcinogens or carcinogen precursors, as exemplified by the positive relationship between aflatoxin ingestion and hepatocellular cancer; (2) effects on the production, activation, or inactivation of carcinogens by the intestinal flora; (3) effects on the endogenous production, activation, or inactivation of carcinogens, as exemplified by the possible modifying effect of dietary protein on the carcinogenicity of ingested nitrosamines; and (4) alterations of tissue susceptibility to carcinogenesis. The latter mechanism may be exemplified by the relationship between the incidence of endometrial cancer and dietary fat or total dietary calories. The following factors are associated with a high risk of endometrial cancer: obesity, early menarche, late menopause, diabetes mellitus, hypertension, infertility, Stein-Leventhal syndrome, previous breast or ovarian cancer, radiation exposure, and estrogen therapy. The first five may stem from a dietary excess of calories or fat, resulting in the excessive endogenous production of estrogens. Although the precise role of estrogens in the genesis of endometrial cancer is uncertain, recent studies indicate that they are probably involved. (53 refs)

78-4863 **The Estrogen-Cancer Hypothesis with Special Emphasis on DES.** (Eng) Hertz, R. (No affiliation given). *In: Human Risk Assessment. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book C), 583 pp.; 1665-1673; 1977.

The genesis of the estrogen-cancer hypothesis, which postulates that both exogenous and endogenous estrogens and their metabolites play a significant role in the pathogenesis of cancer in estrogen-responsive tissues of humans and animals, is reviewed. Numerous studies indicate that estrogen administration is followed by routinely reproducible tumors of the breast, cervix, endometrium, ovary, pituitary, testicle, kidney, and bone marrow in mice, rats, rabbits, hamsters, or dogs. Malignant uterine mesotheliomas have been induced in squirrel monkeys by estrogen administration. A definitive association has been established between maternal exposure to estrogen (diethylstilbestrol) during pregnancy and the development of vaginal adenocarcinomas in their daughters. There is also impressive evidence that endogenous estrogen is related to the pathogenesis of breast and endometrial cancers. The association of endometrial cancer with excessive endogenous estrogen, as in the case of women with Stein-Leventhal disease, suggests a chronic stimulatory effect on this responsive tissue. The effectiveness of progesterone, which directly antagonizes the mitosis-stimulating action of estrogen, in inducing regression of both endometrial carcinoma and endometrial adenomatous hyperplasia also implicates endogenous estrogen as a factor in endometrial cancer. Evaluation of epidemiological data is hampered by a lack of precision in the pathological diagnosis of endometrial cancer, so caution in interpretation is indicated. (55 refs)

78-4864 **Hepatic Tumors and Oral Contraceptives.** (Eng) Fechner, R. E. (No affiliation given). *Pathology Annual* 12(part 2): 293-310; 1977.

Clinical and experimental data linking ingestion of oral contraceptives (OC) with hepatic tumors are reviewed. Comparison of the incidence of focal nodular hyperplasia before and after 1960 (the year OC received Federal Drug Administration approval) disclosed nothing to suggest that focal nodular hyperplasia has increased in frequency or is associated with OC. However, evidence suggests that these lesions may be more prone to rupture in women taking OC. Liver cell adenomas, on the other hand, appear to have increased in frequency since 1960, and the tumors in women taking OC have a tendency to be slightly larger. These tumors have occurred almost exclusively in young women, most of whom had been taking OC for at least 3 yr. A high percentage of the latter used a preparation containing mestranol. The results of ultrastructural and experimental studies are reviewed, along with the occurrence of vascular alterations in women taking OC. (116 refs.)

78-4865 **Liver Adenomas and Oral Contraceptives.** (Eng) Pike, M. C. (Dept. Community Medicine, Univ. Southern California, Los Angeles, CA, 90033); Edmondson, H. A.; Benton, B.; Henderson, B. E. *In: Incidence of Cancer in Humans. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4, 602 pp.; 423-427; 1977.

The association between liver adenomas and oral contraceptives (OC) was investigated in a case-control study of 34 adenoma patients. The frequency of OC use was similar in patients (29/34) and controls (26/34). However, the risk of liver adenomas was clearly associated with duration of use. Of the 29 users, 26 were taking them at the time of diagnosis and 2 others had stopped taking them <2 mo earlier. Twenty-four used mestranol-containing pills only, vs 15 of the controls. (9 refs)

78-4866 **Effects of Oral Contraceptives on Carcinogenesis in the Cervical Epithelium.** (Ger) Soost, H. J. (Institut fur Klinische Zytologie der Technischen, Universitat Munchen, Prinzregentenplatz 14, D-8000 Munich 80, W. Germany); Joswig-Priewe, H. *Arch Geschwulstforsch* 48(4): 345-355; 1978.

Data on the hormonal action of oral contraceptives (OC's) are reviewed. Cytophotometric investigations showed that the DNA levels in uterine cervix cells from women with a long history of OC use were normal. Statistical comparisons, based on cytological and histochemical examinations, among

he women according to type of OC formulation used indicated that some formulations produced high rates of cervical atypia, others low rates of atypia. Only a few women showed a higher rate of dysplasia and carcinoma in situ of the cervix than that in controls. Pinpointing OC's as a cause of cervical carcinogenesis is difficult because of the influence of other factors, especially a change in sexual behavior, on tumor development. At present, OC use cannot be directly related to the increased occurrence of cervical atypia. (72 refs.)

78-4867 **Exogenous Estrogens and the Incidence of Neoplasms in Tissues of Mullerian Origin.** (Eng) Weiss, N. S. (Dept. Epidemiology, Sch. Public Health and Community Medicine, Univ. Washington, Seattle, WA, 98195). *In: Incidence of Cancer in Humans. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4, 602 pp.; 413-421; 1977.

Trends in the incidence rates of cancers of mullerian-derived tissues are discussed. In the 1970's, there were sharp increases in endometrial cancer incidence in a number of areas in the US. These increases closely followed the beginning of a period of rapidly rising consumption of estrogen preparations by menopausal women. Endometrial cancer is more prevalent among women with high circulating levels of endogenous estrogens, and recent studies have shown increased rates among menopausal women using exogenous estrogens and women receiving stilbestrol. The nature of many of the lesions being produced by estrogen use remains unknown, but it is likely that menopausal estrogens play an etiologic role in endometrial cancer. Relative frequencies and incidence rates of endometrioid-clear cell tumors in three areas of the US increased between 1969 and 1974; these increases also followed increased estrogen consumption. The incidence of other epithelial ovarian tumors has not changed appreciably since the late 1940's. The relationship of contraceptive estrogens to endometrial cancer or any of the estrogens to the occurrence of endometrioid and clear cell ovarian tumors has not been established. (27 refs)

78-4868 **How Safe Is Nuclear Power (Letter to Editor)?** (Eng) Diesendorf, M. (20 Earle St., Lyneham, Australian Capital Territory 2602, Australia). *Med J Aust* 1(3): 162-163; 1978.

Comparisons of the health hazards of plutonium and radium are meaningful only for bone cancer, and bone should not be assumed to be the critical organ for Pu. ^{239}Pu produced lung cancers in dogs exposed to 0.2-1.0 μCi. In bone cancer experiments, ^{239}Pu was 5-10 times more toxic than ^{226}Ra. Ra is deposited uniformly throughout the bone, but Pu accumulates on the bone surface, where cells at highest risk for tumors are located. Human epidemiological investigations have also implicated Pu in several cancers. Some human health hazard exists at every stage of Pu processing. (11 refs)

78-4869 **The Real Death Rays.** (Eng) Saldinger, E. (Calhoun Coll.). *Yale Scientific* 52(4): 16-21; 1978.

The various biological effects of different types of radiation are surveyed. The long-term effects of radiation were studied in Japanese survivors of the Hiroshima and Nagasaki bombings. The Hiroshima group showed a high incidence of leukemia that peaked at 30 times the av incidence. It usually appeared about 10 yr postirradiation. In addition, the incidence of cancer of the stomach, lung, breast, cervix, and ovary in these subjects was two to four times the av rate. Background radiation, ie, UV rays and cosmic rays, is associated with an increased incidence of skin cancer. Therapeutic radiation can be damaging to fetuses and to patients. Leukemia and thyroid cancer have occurred in people irradiated as children for enlarged thymus glands. Moderate amounts of radiation may cause premature aging and a shortened life-span. Ion production and the amount of energy absorbed by different tissues, six types of ionizing radiation with potential to destroy living tissue, and the molecular effects of radiation are also reviewed, along with the effects of radiation at the cellular level. Lymphocytes show high sensitivity to radiation, and in Hiroshima and Nagasaki the lymphocyte level in the population only returned to normal 3-4 yr after the bombing. (no refs)

78-4870 **Carcinogenic Effects of Medical Irradiation.** (Eng) Hutchison, G. B. (Dept. Epidemiology, Harvard Sch. Public Health, Boston, MA, 02115). *In: Incidence of Cancer in Humans. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4, 602 pp.; 501-509; 1977.

The carcinogenic risk to human populations associated with medical irradiation is discussed. Epidemiologic studies of several types of cancer that have developed after medical irradiation are reviewed. Ionizing radiation at any but the highest levels of exposure appears to be capable of inducing malignant transformation. Empiric approaches cannot identify an absolutely safe dosage level, although the hazard at arbitrarily small doses may be expressed in terms of probability concepts. Simple linear models of radiation effects give satisfactory fits to most human data, but linear interpolation on dose may systematically overestimate effects at doses $\geq$10 rads. Most observations of radiation effects in human populations involve high doses, high dose rates, and low-linear energy transfer (LET) radiation; and with this type of exposure, departure from linearity is expected. Less extensive data are available on high-LET exposure at high dose levels, and lin-

ear interpolation on these data may give adequate estimates of low dose effects at high LET. Generally, it will not be satisfactory to determine the relative effects of high- and low-LET radiations at high dose rates and employ this relation in estimating effects of low-LET radiation at low doses. Because of the nonlinearity of effect with low-LET radiation, this procedure will systematically overestimate the effect. (25 refs.)

78-4871 **The Risks for Radiation Workers.** (Eng) Rotblat, J. (Dept. Physics, Univ. London, London, England). *Bull At Sci* 34(7): 41-46; 1978.

The fact that, in 1977, the International Commission on Radiological Protection did not find it necessary to reduce the max permissible dose limit for radiation workers [5 roentgens-equivalent-man (rem)/yr] is discussed. The survivors of the Hiroshima and Nagasaki bombings are generally assumed to be the most reliable material for determining a reasonable estimate of the risk factor for radiation-induced cancer. However, for all types of cancer except leukemia, the risk factors calculated from the Japanese survivors are significantly lower than those from other populations. The survivors may not be suitable, therefore, as a basis for calculating radiation risk factors for other populations. There appears to be a need to revise upward the risk factors for cancer induction, and it is suggested that the present dose limit for radiation workers be reduced by a factor of 5. Furthermore, a worker who receives more than 1 rem/yr should be eligible for compensation, should he incur a disease that might be attributable to his exposure to radiation. (10 refs.)

78-4872 **Cancer and Low Level Ionizing Radiation.** (Eng) Morgan, K. Z. (Sch. Engineering, Georgia Inst. Technology, Atlanta, GA). *Bull At Sci* 34(7): 30-41; 1978.

The risk of cancer from low-level exposure to ionizing radiation is discussed. Since 1960, an overwhelming amount of data have shown that there is no safe level of exposure and that there is no dose of radiation so low that the risk of malignancy is zero. The risk of cancer induction from radiation exposure increases more or less with the increase or accumulation of radiation exposure. Because of many individual characteristics (eg, genetic inheritance, sex, disease, and eating habits), certain members of the general population have a higher risk of radiation-induced malignancies than others. The risk of cancer induction at low doses of radiation may be as great or greater for the human race than genetic risk. Several reasons why, in many cases, use of the linear hypothesis to estimate risk at low doses is not conservative are given. The medical profession and not the nuclear industry is the real culprit with respect to unnecessary exposure of the population to radiation. It is suggested that the max permissible exposure should be reduced by a factor of 2 and, perhaps later, by a factor of 10 if it can be shown that all unnecessary exposure (especially medical) can be reduced and that there will be a net benefit to mankind by such action. (27 refs.)

78-4873 **Radiation Effects.** (Eng) Upton, A. C. (Dept. Pathology, State Univ. New York, Stony Brook, NY, 11594). *In: Incidence of Cancer in Humans. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4, 602 pp.; 477-500; 1977.

An association between radiation and neoplasia has been detected in human populations at lower levels of exposure than heretofore suspected. However, the dose-incidence relationship cannot be specified precisely for any neoplasm, and the relation may vary depending on factors such as the type of neoplasm and age at irradiation. Susceptibility varies widely among different organs and under the influence of genetic and physiological factors. The interaction of constitutional, environmental, and radiologic variables influences the dose-incidence relationship in laboratory animals. Although the pathogenesis of radiation-induced neoplasms is poorly understood, a variety of mechanisms has been postulated, including somatic mutation, virus activation, and disturbances in homeostasis. A succession of changes requiring a relatively long latent period seems to be involved in many cases. Because quantitative assessment of the risk of radiation-induced cancer in humans must be based primarily on human dose-incidence data, epidemiologic follow-up study of irradiated human populations remains essential. (88 refs.)

78-4874 **Epidemiology of Radiation-induced Malignant Human Tumors.** (Rus) Strel'tsova, V. N. (No affiliation given). *Med Radiol (Mosk)* 23(8): 83-90; 1978.

Epidemiological data on malignant human tumors induced by ionizing radiation are reviewed. The bone marrow, thyroid gland, lymph nodes, reticular tissue, pharynx, bronchi, pancreas, and stomach are most susceptible to the carcinogenic effects of such radiation. (23 refs.)

78-4875 **Radiation Carcinogenesis In Vitro: Implications for Mechanisms.** (Eng) Little, J. B. (Dept. Physiology, Harvard Univ. Sch. Public Health, Boston, MA, 02115). *In: Mechanisms of Carcinogenesis. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Har-

or: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book B), 699 pp.; 923-939; 1977.

Data on the induction of malignant transformation in C3H mouse embryo fibroblast cells by x-rays and UV light are reviewed. X-ray transformation can be divided into two steps: (1) fixation of the transformed state as a heritable cellular property, and (2) expression of this damage in terms of morphologically altered cells. The transformation frequency rises rapidly with increasing radiation dose in the range below 400 rads; at this point it reaches a plateau that remains constant up to 1,500 rads. The dose-response curve for transformation induction by UV light is similar to that for x-rays, with an inflection point at 75 ergs/mm². If transformation frequency is plotted as a function of time after irradiation, when the cultures are dispersed and seeded at low cell density, the transformation frequency per viable cell rises rapidly, reaching a max with a repair time of 3 hr. With longer repair intervals, the transformation frequency falls and is very low or not detectable if the cells are not stimulated to divide within 48 hr of irradiation. Expression of the transformed state requires about 12 additional rounds of cell division. Exposure during this expression period to a number of noncarcinogenic agents may either greatly enhance (12-O-tetradecanoylphorbol-13-acetate or interferon) or markedly suppress (Amphoterecin-B) transformation. It is concluded that appropriate stimuli and capacity for cell proliferation in irradiated cell populations are major determinants in the fixation and expression of transformational damage and that the ultimate carcinogenic effect of radiation depends largely on factors secondary to the initial DNA damage. (32 refs)

78-4876 **Melanoma and Solar Radiation.** (Ger) Herrmann, W. P. (Universitats-Hautklinik, Joseph-Stelzmann-Strasse 9, 5000 Koln 41, W. Germany). *Dtsch Med Wochenschr* 103(29): 1155-1156; 1978.

Epidemiological studies not only suggest a relationship between exposure to sunlight and the incidence of skin melanoma, but show a genetic predisposition as well. Ultraviolet radiation is a possible cofactor in the genesis of malignant melanoma. (14 refs.)

78-4877 **Ultraviolet Radiation as a Cause of Cancer.** (Eng) Scott, E. L. (Statistical Lab., Univ. California, Berkeley, CA, 94720); Straf, M. L. *In: Incidence of Cancer in Humans. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4, 602 pp.; 529-546; 1977.

The role of UV radiation in the production of human skin cancer is reviewed. There is a strong association between UV flux and the incidence and mortality rates of skin cancer (both melanoma and nonmelanoma) for both sexes and all age groups. The carcinogenesis of skin cancer is uncertain, however, and it may be complicated by a complex UV repair mechanism. The dose-response relationship is not known. In principle, it can be estimated from the data on skin cancer by sex and age for different localities where the UV flux is known, but available observations are unreliable and incomplete. Estimates of the expected rate of skin cancer corresponding to a 20% increase in UV flux or a 10% depletion of stratospheric ozone indicated that there is a strong effect of UV flux and that it persists even when other possible predictors are taken into account. The numerical value of the estimated increase in melanoma was frequently greater than that for nonmelanoma. Although both temperature and pigmentation play a role in the etiology of skin cancer, UV flux is the most important factor. Corresponding calculations for cancer of the eye and lip are less reliable due to a sparsity of data. (37 refs.)

78-4878 **Radiation Induced Leukemia and Leukopenia in the Lizard *Uromastix hardwickii* (Preliminary Information).** (Eng) Ahmad, M. (Dept. Physiology, Univ. Karachi, Karachi-32, Pakistan); Taqawi, I. H. *Radiobiol Radiother (Berl)* 19(3): 353-360; 1978.

Spiny-tailed lizards (*Uromastix hardwickii*) were exposed to 0, 3,000, 3,500, or 4,000 R of ^{60}Co-γ irradiation, and their WBC count was monitored for 6 wk. Lizards with no exposure maintained a WBC count of almost 17,600/mm³ during the entire experiment. In lizards exposed to 3,000 R, the mean WBC count was 14,000/mm³ at the end of wk 1 and 20,600/mm³ in wk 6. In the group exposed to 3,500 R, the mean WBC count at the end of wk 1 was 13,800/mm³, but it decreased to 4,400/mm³ in wk 6. In animals exposed to 4,000 R, the mean WBC count was 8,600/mm³ at the end of wk 1 and 1,600/mm by wk 6. These observations, combined with those of previous studies, indicate that the WBC elevation in the group exposed to 3,000 R, after the initial decrease during the wk 1, was due to abnormal cell morphology. Thus, the 3,000 R dose induced leukemia and the higher doses induced leukopenia. (20 refs.)

78-4879 **An Analysis of Radiation-induced Malignancy Based on Somatic Mutation.** (Eng) Leenhouts, H. P. (Assoc. Euratom-ITAL, Postbus 48, Wageningen, Netherlands); Chadwick, K. H. *Int J Radiat Biol* 33(4): 357-370; 1978.

A mathematical equation is derived to provide a general description of the dose response for radiation-induced malignancy. The equation is based on the molecular theory of cell survival and on the proposal that a somatic mutation in the normal dominant homologous gene of a diploid cell, which

carries the malignant factor, may allow expression of a recessive malignant factor. The equation assumes that a radiation-induced DNA double-stranded break can cause a somatic mutation or a chromosome aberration that may leave the cell in a precancerous state. Data on the radiation-induced transformation of diploid cells and on the transformation of tetraploid cells are analyzed. The results indicate that the dose relationship for cell transformation is strictly nonlinear, increases linearly-quadratically to a max, and decreases at higher doses. Therefore, any type of extrapolation from high dose measurements to levels of interest for radiological protection should be treated with caution. (72 refs)

78-4880 **Expression of RNA Tumor Viruses at Translation and Transcription Levels.** (Eng) Fan, H. (Tumor Virology Lab., Salk Inst., P.O. Box 1809, San Diego, CA, 92112). *Curr Top Microbiol Immunol* 79: 1-41; 1978.

Data on the translation and transcription of RNA tumor virus-specific RNA, especially that of avian and murine C-type RNA tumor viruses, in infected and uninfected cells are reviewed. Most of the virus-specific RNA in cells is identical in sequence to virion RNA, with only small amounts complementary to virion RNA being present. Intracellular virus-specific RNA is 35S and 20S-30S in size. Virus-specific RNA is synthesized in the nucleus by nuclear RNA polymerase II. The 35S molecule is the major virus-specific RNA synthesized; no large precursor molecules are evident, although larger size virus-specific RNA does exist. Cytoplasmic virus-specific RNA serves as a messenger RNA (mRNA) for viral proteins, and it is packaged into virus particles; however, only a minority of this RNA serves as mRNA. The major mRNA molecule has a size of 35S, and evidence indicates that the internal structural proteins of the virus are synthesized on polyribosomes containing 35S virus-specific mRNA. RNA coded by endogenous C-type virus genes is expressed at low levels in uninfected cells, and the level of this RNA is frequently correlated with the expression of viral proteins. Furthermore, partial expression of a particular endogenous virus may occur. DNA sequences that correspond to sarcomagenic portions of avian and murine sarcoma viruses are present in uninfected cell DNA. In some cases, transcription of the DNA into RNA is correlated with the growth state of the cell. (135 refs.)

78-4881 **Temperature-sensitive Mutants of Avian RNA Tumor Viruses: A Review.** (Eng) Friis, R. R. (Institut fur Virologie, Justus-Liebig-Universitat Giessen, Fachbereich Humanmedizin, Frankfurter Strasse 107, D-6300 Giessen, W. Germany). *Curr Top Microbiol Immunol* 79: 261-293; 1978.

A review of temperature-sensitive mutants of avian RNA tumor viruses is presented. To date, at least one temperature-sensitive mutant has been identified for each genetic element of the avian sarcoma viruses. In this review, the mutants have been grouped into two categories: T mutants, which have defects exclusively in transformation, and R mutants, which are defective for virus replication, even if the function affected is also essential for transformation. Concerning T mutants, specific topics discussed include the uncertainties about the nature of the transforming gene *src*, parameters for measuring transformation, transformation-defective and partially transformation-defective mutants, and speculations about the function(s) of the *src* gene product. Specific topics discussed concerning R-mutants include mutants defective for *env*, *pol* mutants, and a mutant defective for *gag*. (156 refs.)

78-4882 **The Function and Origin of the Transforming Gene of Avian Sarcoma Virus.** (Eng) Varmus, H. E. (Dept. Microbiology, Univ. California, San Francisco, CA, 94143); Spector, D. H.; Deng, C. T.; Padgett, T.; Bishop, J. M.; Stehelin, D.; Stubblefield, E. *In: Mechanisms of Carcinogenesis. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book B), 699 pp.; 1159-1168; 1977.

Studies on the origin and function of the transforming gene (*src* gene) of avian sarcoma virus (ASV) using DNA complementary (cDNA) to a portion of the genome that includes some or all of the *src* gene (cDNA-*sarc*) are reviewed. In ASV-infected avian cells (which are permissive for virus replication), large amounts of RNA transcripts containing the *src* gene are detected readily. cDNA-*sarc* anneals to both 35S and 24S RNA in these cells, but it is not known which of these species serves as a messenger in the translation of the *src* gene product. Reversion of ASV-transformed baby hamster kidney (BHK) cells to normal behavior appears to be related to relatively small differences in expression of the *src* gene, as revealed by cDNA-*sarc* hydridization experiments. Annealing of cDNA-*sarc* to nucleic acids from normal (uninfected) cells established that DNA related, but not identical, to the *src* gene of ASV is present in the genomes of all vertebrates. RNA's extracted from a large variety of avian tissues and cells have been tested for their capacity to hybridize with cDNA-*sarc*; in every case, the results indicate the presence of 1-8 "sarc" RNA molecules per cell. When the distribution and size of sarc-containing RNA were compared in normal Japanese quail embryo fibroblasts and in cells derived from a fibrosarcoma induced in quail with methylcholanthrene, virtually identical concentrations of sarc RNA were found in the nuclear, cytoplasmic, and polyribosomal fractions. The function of the sarc sequence remains unknown. (33 refs)

78-4883 **Type C Viruses of Wild Mice: Characterization and Natural History of Amphotropic, Ecotrop-**

c, and Xenotropic MuLV. (Eng) Gardner, M. B. (Dept. Pa-nology, Univ. Southern California Sch. Medicine, Los An-eles, CA, 90033). *Curr Top Microbiol Immunol* 79: 215-259; 978.

Experiments dealing with the discovery of low- and igh-virus-expressor wild mice, the characterization of am-hotropic (A-tropic), ecotropic (E-tropic), and xenotropic X-tropic) C-type murine leukemia viruses (MuLV) in wild nice, and the natural history of C-type viruses in wild mice re reviewed. C-type viruses exist in most wild mice in a trongly suppressed state; virus activation is found primarily n association with lymphomagenesis in old age. In some nice, however, latent C-type virus is genetically less sup-ressed and is manifest as a congenitally transmitted, persist-nt infection with specific immune tolerance, associated with n increased incidence of non-T-cell lymphoma and hind imb paralysis. The A-tropic viruses are the most prevalent nd they are unique to wild mice. The E-tropic viruses are solated mainly from paralyzed and some lymphoma-bearing vild mice. X-tropic virus has been isolated from two ododeoxyuridine-treated embryo culture. The A-tropic virus robably represents the ancestral virus of these classes. Ex-erimental transmission in newborn laboratory mice indi-cates that A- and E-tropic viruses are lymphomagenic, but nly the latter are paralytogenic. Autogenous humoral im-nunity to indigenous MuLV of all three virus classes is ap-arently lacking in both high- and low-expressor wild mice. However, the role of autogenous humoral and cellular im-nunity in these mice is still uncertain. The virus characteris-ics, natural history, and associated diseases in high-expressor LC wild mice are different in several major aspects from those n high-expressor lymphoma-prone AKR laboratory mice. Lymphoma and paralysis can be controlled in LC wild mice by suppression of E- and A-tropic viruses, using specific gen-etic and immunologic measures. (143 refs.)

78-4884 **The Development of Vaccines Against Feline Leukemia.** (Eng) Jarrett, W. F. (Dept. Veteri-nary Pathology, Univ. Glasgow Veterinary Sch., Bearsden, Glasgow G61 1QH, Scotland). *In: Mechanisms of Carcino-genesis. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book B), 699 pp.; 1215-1222; 1977.

Vaccines have been developed and successfully tested against felineleukemia. This disease lends itself to these approaches because feline leukemia virus (FeLV) is transmitted horizon-tally, cats are usually infected until they are young adults (5 mo), and a natural immunosurveillance system exists. Cats inoculated with 2×10^9 infected cultured cells developed high antibody titers that persisted for >1 yr. These cats were viremic, and virus was found in the bone marrow at necropsy. In contrast, cats inoculated with 4×10^7 cells produced a good feline oncornavirus-associated membrane antigen (FOCMA) antibody response, and no virus was found in tissues taken at necropsy. In other experiments, cats were inoculated with FL74 cells (having a high density of antigen on the surface and pro-ducing virus of low infectivity) and challenged with 10^7 IU of FeLV 7 mo later. No abnormality was found in the cats, and no virus was found in any tissues. The most promising vaccine to date has been prepared from FL74 cells inactivated by paraformaldehyde. Animals inoculated with this vaccine (7×10^7 treated cells) have shown complete resistance to challenge. It is concluded that the pathogenesis and epidemiology of FeLV infection make vaccination practi-cable and that the feasibility of large-scale field vaccination is now essentially a technological exercise. (8 refs)

78-4885 **Leukemia, Lymphoma, and Fibrosarcoma of Cats as Models for Similar Diseases of Man.** (Eng) Essex, M. (Dept. Microbiology, Harvard Univ. Sch. Public Health, Boston, MA, 02115); Cotter, S. M.; Stephen-son, J. R.; Aaronson, S. A.; Hardy, W. D. *In: Mechanisms of Carcinogenesis. Proceedings of the Cold Spring Harbor Con-ferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Har-bor Laboratory): Origins of Human Cancer. Vol. 4 (Book B), 699 pp.; 1197-1214; 1977.

The use of spontaneous feline leukemia, lymphoma, and fi-brosarcoma as models for studying analogous human tumors is reviewed. There is overwhelming evidence from epidemi-ologic and serologic studies that spontaneous leukemia and lymphoma of cats are caused by horizontally transmitted viruses [feline leukemia virus (FeLV)]. In studies with feline fibrosarcoma, a correlation was found between the presence of antibodies to feline oncornavirus-associated cell-mem-brane antigen (FOCMA) and tumor progression. In subse-quent studies of laboratory and household cats, animals that did not develop malignancies following exposure to FeLV or feline sarcoma virus had elevated titers of FOCMA antibo-dies. A number of independent studies provide evidence that FOCMA is distinct from the major virus proteins, gp70 and p30. It is concluded that immunosurveillance works, at least for one group of tumors in one mammalian species. There-fore, attempts to determine if immunosurveillance ever oc-curs in humans should not be abandoned. (47 refs)

78-4886 **Progress in Studies on the Etiology and Serolog-ic Diagnosis of Enzootic Bovine Leukosis.** (Eng) Mussgay, M. (Federal Res. Inst. Animal Virus Diseases, Paul Ehrlich Strasse 28, D-7400 Tubingen, W. Germany); Kaad-en, O. R. *Curr Top Microbiol Immunol* 79: 43-72; 1978.

Advances made since 1969 concerning the properties of bo-vine C-type particles and their use in the serologic diagnosis of enzootic bovine leukosis are reviewed. This disease is cha-racterized by neoplasia of the lymphocyte-forming tissue and

by its occurrence as multiple cases within a herd. It may develop in two phases: a persistent lymphocytosis followed, in approx 10%-30% of the animals, by the formation of leukotic tumors. According to the literature, the incubation time varies between 200 days and 7 yr. Etiologic studies dealing with epizootiological aspects of the disease, experimental transmission, and the production of bovine C-type particles in cell culture are reviewed. Attention is also focused on the biochemical and biophysical properties of the virus particles, their morphology, genetic relatedness to host DNA, host spectrum, and their relationship to other retroviridae. Serologic diagnoses by agar gel immunodiffusion, complement fixation, immunofluorescence, radioimmunoassay, and the indirect immunoperoxidase test and the detection of both the virus and its antigen are summarized. (98 refs.)

78-4887 **Current Assessment of Human Health Hazards Associated with Bovine Leukemia Virus.** (Eng) Van Der Maaten, M. J. (U.S. Dept. Agriculture, Agricultural Res. Service, North Central Region, Natl. Animal Disease Center, Ames, IA, 50010); Miller, J. M. *In: Mechanisms of Carcinogenesis. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book B), 699 pp.; 1223-1234; 1977.

The properties of bovine leukemia virus (BLV) are reviewed, along with the potential hazards of this virus to human health. Seroepidemiologic studies have provided ample evidence of the association between virus infection and tumor development. Morphologic, biochemical, and immunologic studies have indicated that BLV is a unique oncornavirus that is not endogenous to the bovine species. The presence of infectious BLV in milk was established by studies in which sheep, inoculated with milk from infected cows, subsequently developed active BLV infections. Circumstantial evidence that exposure to milk or cattle may result in an increased incidence of human neoplasms has come from the occurrence of an unusual number of cases of adult nonlymphocytic leukemia in a community with a commercial milk-drying plant. Several cases of lymphoid leukemia have been reported in people living near a dairy herd with numerous cases of lymphosarcoma. Other studies, however, have not supported this correlation. Studies with chimpanzees inoculated with large doses of cell-culture-grown BLV have provided direct proof of primate susceptibility. Tests of sera from cancer patients, high-incidence cancer families, and individuals with max exposure to infected cattle or to BLV in the laboratory have failed to identify even one individual with antibodies to BLV. Thus, the risk to human health associated BLV would seem to be minimal. (57 refs)

78-4888 **Herpes Simplex Viruses and Human Malignancies.** (Eng) Rawls, W. E. (Dept. Pathology, McMaster Univ., Hamilton, Ontario L8S 4J9, Canada Adam, E. *In: Mechanisms of Carcinogenesis. Proceedings the Cold Spring Harbor Conferences on Cell Proliferatio* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Sprin Harbor: Cold Spring Harbor Laboratory): Origins of Huma Cancer. Vol. 4 (Book B), 699 pp.; 1133-1155; 1977.

Results of a seroepidemiologic case-control study of wome with cervical cancer (CC) are presented and compared wit published data relating herpes simplex virus type 2 (HSV-2 to CC. Sera were collected from 285 white women (108 wit invasive carcinoma, 71 with carcinoma in situ, and 106 con trols with no cervical disease). Forty-five percent of the can cer patients and 17% of the control women had antibodie to HSV-2. Forty-four percent of the invasive cancer cases 42% of the carcinoma in situ cases, and 30% of the control had multiple sex partners. These figures are comparable t those from other studies. Antibodies to HSV-2 were mor common among women with multiple sex partners tha among women with one sex partner. Data from several stu dies using serologic assays to determine past infections wit HSV-2 indicate that few, if any, women with CC have no been infected with at least one of the herpes simplex viruses Studies of the interrelations among sexual promiscuity, CC and HSV-2 suggest that the association between HSV-2 and CC does not simply represent one of covariability to sexual promiscuity. In addition to neutralizing antibodies, antibodies to three other virus-induced antigens (AG-4, HSV tumor-associated antigen, and VP134) have been detected in sera from women with CC. HSV-2 DNA and proteins have not been easily and reproducibly demonstrated in CC cells. It is not yet possible to establish an unequivocal etiologic relationship between HSV-2 and CC. (81 refs)

78-4889 **Papillomaviruses: Possible Role in Human Cancer.** (Eng) Orth, G. (Unite de Recherche sur l'Etiologie Virale des Cancers Humains, Laboratoire Associe au CNRS no. 147, Unite 140 de l'INSERM, Institut Gustave-Roussy, 94800 Villejuif, France); Breitburd, F.; Favre, M.; Croissant, O. *In: Mechanisms of Carcinogenesis. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book B), 699 pp.; 1043-1068; 1977.

Data on the biological properties of animal and human papillomaviruses (PV) are reviewed to show that a role of PV in the origin of human cancer must be considered. At least 13 different PV have been characterized in benign skin or mucosa tumors of one bird species and nine mammalian species. Three of these animal PV have oncogenic potential for epithelial or connective tissues in both natural and experimental conditions. When oncogenic, PV induce premalignant lesions that convert to malignancy under the influence of multiple factors, such as host and perhaps virus genetic constitution, deficient host immune response, and environmental cocar-

ogenic factors. The formation of a papilloma results from abortive transforming infection of germinal cells. Human -induced conditions include skin warts, epidermodysia verruciformis, condylomata acuminata, oral papilnas, and juvenile laryngeal papillomatosis. Lesions are usuy benign and they usually regress, but malignant nsformation may occur as a rare event. It has long been nsidered that the different human lesions are due to the ne virus and that the clinical types are determined by local nditions, but evidence is now accumulating that several ferent human PV may be involved. (124 refs)

-4890 **Human Papovaviruses.** (Eng) Takemoto, K. K. (Lab. Viral Diseases, Natl. Inst. Allergy and Infectious Diseases, NIH, Bethesda, MD, 20014). *Int Rev Exp thol* (18): 281-301; 1978.

rrent knowledge of the biology, biochemistry, and ongenicity of human papovaviruses (PVs) is reviewed. Of the ree types of related but immunologically distinct PVs isoed from humans, only BK virus and JC virus are true man viruses. The third type [represented by 2 isolates from progressive multifocal leukoencephalophathy (PML) case d 1 from melanoma tumor tissue] can be classified as simi virus 40 (SV40) variants that are rare and of unknown igin. JCV is probably the causative agent of PML. It has en isolated from or identified in diseased brain tissue of 21 ses. BKV has been found in the urine of immunosuppressed tients. There are at least 10 isolates from the urine of renal ansplant patients and 3 from Wiskott-Aldrich cases. There no known disease associated with BKV. PVs, their antins, or viral DNA sequences have been detected in some man tumor cells, but there is no conclusive evidence that ese viruses play any significant role in human tumor cells. KV, JCV, and SV40 are distantly related primate PVs based the following observations: (1) their capsid antigens show me serologic cross-reactivity in several different types of sts, and they induce similar or identical T antigens; and (2) e DNAs of the three viruses show 10%-25% homology. 05 refs)

3-4891 **The Human Papovaviruses and Their Potential Role in Human Diseases.** (Eng) Khoury, G. Lab. DNA Tumor Viruses, NCI, NIH, Bethesda, MD, 0014); Lai, C. J.; Solomon, D.; Israel, M.; Howley, P. *In: Mechanisms of Carcinogenesis. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watn, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold pring Harbor Laboratory): Origins of Human Cancer. Vol. (Book B), 699 pp.; 971-988; 1977.

tudies of simian virus 40 (SV40) and human papovaviruses PVV) arereviewed. Two PVV have been isolated from huans: (1) JC, from the brain of a patient with progressive multifocal leukoencephalopathy (PML): and (2) BK, from the urine of an immunosuppressed renal transplant patient. Although antibodies to SV40 are uncommon in humans (3%), antibodies to both BK and JC viruses are prevalent. The human PVV induce the synthesis of a tumor (T) antigen early in the lytic cycle and in transformed cells. The BK and JC T antigens cross-react strongly with the SV40 T antigen. Tumor-specific transplantation antigens (TSTA) of PVV have been localized on the surfaces of transformed and tumor cells. Structural or virus antigens can be detected late in the lytic cycle and are absent in transformed cells in which only the early events of PVV-cell interactions are expressed. Both JC and BK viruses induced tumors in inoculated newborn hamsters, and BK virus has malignantly transformed animal cells in tissue culture. Papovalike particles were detected by electron microscopy or immunoreactivity with SV40 T antisera in human meningiomas and a metastasis from a malignant melanoma. The association of JC virus with PML seems firmly established. PVV particles have been detected in the brains of almost every patient with this disease and have been specifically localized in the areas of demyelination. All but two isolates from these lesions have been JC virus. A degenerative neurologic disease, pathologically identical to PML in humans, has been described in macaques. Virus isolates from two cases were identified as SV40. Thus, SV40 and JC virus appear to be associated with rare but pathologically similar diseases in their natural hosts. (96 refs)

78-4892 **The Role of the Papovavirus Gene *A* in Oncogenic Transformation.** (Eng) Tegtmeyer, P. (Dept. Microbiology, State Univ. New York, Stony Brook, NY, 11594); Rundell, K. *In: Mechanisms of Carcinogenesis. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book B), 699 pp.; 957-969; 1977.

Studies of the complementation group A mutants of simian virus 40 (SV40) and polyoma virus, which are defective in both productive and transforming infections, are reviewed. Studies of SV40 infection have identified the *A* gene as necessary for the initiation and perhaps the maintenance of neoplastic transformation in model animal systems. The localization of the A-protein binding site to a region of viral DNA that is functionally important for both DNA replication and transcription suggests that the A protein may regulate these processes in a direct and coordinated way. Cross-reacting antigens have been detected in cells productively infected or transformed by SV40 or by human strains of papovaviruses. Immunoprecipitation confirmed that the antigen induced by the human virus is closely related to the A protein of SV40. The A proteins specified by SV40 and by RFV strains of human virus in transformed hamster cells are similar but show distinct differences in their peptide patterns, indicating that the A protein is coded for by the virus rather than the

cell. The close functional and structural relationship of the A proteins of SV40 and human viruses suggests that events known to occur in SV40 infection might also be common events in humans during infection by papovaviruses. (74 refs)

78-4893 **BK, A Human Polyoma Virus -- Its Biology, Biochemistry, and Association with Human Tumors.** (Eng) Major, E. O. (Dept. Microbiology, Stritch Sch. Medicine, Maywood, IL, 60153); Fiori, M.; di Mayorca, G.; Zacharias, C. *In: Mechanisms of Carcinogenesis. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book B), 699 pp.; 989-1007; 1977.

Initial investigations of BK virus, a human papovavirus, from its isolation to its association with human disease are reported. BK virus was isolated from the urine of a renal allograft recipient. Antibodies to BK (and to another human papovavirus, JC virus) have been found in 80% of the world population from age 5 to adult. Hemagglutination inhibition (HAI) and plaque neutralization (PN) assays indicate no relationship between BK virus and polyoma virus and only marginal cross-reactivity between BK and SV40 or JC virus. Virion protein analysis by electrophoresis on polyacrylamide gels indicates that BK virus is an independent human isolate and not a simian variant. Molecular hybridization data from experiments in which BK DNA was hybridized with SV40 and JC viral DNA show 10%-40% homology, which exists between sequences located in the late region of the genome. BK virus transforms baby hamster kidney (BHK) cells, and these cells can induce tumors in adult hamsters. BK tumor (T) antigen cross-reacts with other papovavirus T antigens but retains a BK-unique antigenic site. Under single-cycle conditions, the growth cycle of BK virus in the most permissive host, human embryonic kidney cells, takes 48 hr. There is evidence that BK virus remains encapsidated in the nucleus of infected cells for at least 24 hr, so that some host factors must control the timing and extent of virus multiplication. Reassociation kinetics indicate that the number of genome equivalents varies from < 1 to > 3 in the different clones of BK-transformed hamster cell DNA tested. (46 refs)

78-4894 **The Molecular Basis of Transformation by Simian Virus 40.** (Eng) Martin, R. G. (Lab. Molecular Biology, Natl. Inst. Arthritis, Metabolism, and Digestive Diseases, NIH, Bethesda, MD, 20014); Persico-DiLauro, M.; Edwards, C. A.; Oppenheim, A. *Miami Winter Symp* 14: 87-102; 1977.

A model for the molecular basis of cell transformation by simian virus 40 (SV40) is presented. The model assumes that the SV40 tumor (T) antigen is the only viral product required for transformation and that the T antigen is an initiator of viral DNA synthesis. The model proposes that: (1) the T antigen acting at the end of G_1 drives cells into DNA synthesis under suboptimal growth conditions; (2) the host partly regulates the expression of T antigen; (3) T antigen initiates DNA synthesis in the host either by virtue of its high- or low-affinity binding to DNA; and (4) membrane changes are largely secondary to the inability of transformed cells to enter the resting state. (65 refs)

78-4895 **Viruses as Causes of Some Human Tumors? Results and Prospectives of the Epidemiologic Approach.** (Eng) de-The, G. (Unit Biological Carcinogenesis, International Agency Res. Cancer, 69008 Lyon, France). *In: Mechanisms of Carcinogenesis. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book B), 699 pp.; 1113-1131; 1977.

Epidemiologic approaches to the study of viruses as possible causes of human cancer are reviewed, and evidence linking Epstein-Barr virus (EBV) to Burkitt's lymphoma (BL) and nasopharyngeal carcinoma (NPC) is presented. Epidemiologic characteristics of human tumors that would favor the possibility of a viral infection are: (1) horizontal transmission of tumor risk; (2) clustering of tumors in time and/or space; (3) an association between benign viral lesions and specific tumors; and (4) the association between hereditary or genetic factors with the risk for certain tumors. A prospective serological study of BL in 42,000 Ugandan children, 12 of whom developed BL, indicates the probability of EBV infection at an early age in children who develop BL and that antibodies to EBV 7-20 mo prior to clinical onset do not protect against BL. This study plus other observations suggests that a series of causal factors is involved in BL development in tropical areas, including neonatal EBV infection, genetic translocation in chromosome 14 in cells earmarked for malignant transformation, and hyperholoendemic malaria. A fourth unknown factor that represents the triggering event leading to the clinical onset of the disease is postulated. Patients with NPC exhibit similar and even higher EBV serologic reactivities than BL patients. Of even more critical etiologic importance is the presence of EBV markers in epithelial tumor cells. Human tumors that may be virus-associated and would be good candidates for epidemiologic studies include genital cancers (herpes simplex virus type 2, cytomegalovirus, and papillomaviruses); leukemias; lymphomas; and sarcomas; breast carcinoma; and liver carcinoma. (72 refs)

78-4896 **The Biology of EB Virus (Meeting Abstract).** (Eng) Pope, J. H. (Queensland Inst. Medical Res., Australia). *Pathology* 10(2): 190; 1978. (no refs)

-4897 **Viral Etiology of Cancer.** (Spa) de Pasqualini, C. D. (Seccion Leucemia Experimental, Instituto de Investigaciones Hematologicas, Academia Nacional de Medicina, Buenos Aires, Argentina). *An Acad Nac Cienc Exactas Fis Nat Buenos Aires* 29: 229-251; 1977.

udies of the viral etiology of cancer are reviewed. Certain NA and RNA viruses induce cancer in many animal species, including primates. There is indirect evidence of a viral ology for many human tumors. Leukemia with oncorvirus replication was induced in rats and primates by oculation of these animals with human neoplastic material. humans, C particles were found in association with leumia, and replicating B particles were found in breast carnoma cell lines. Oncornavirus was detected in human cans by molecular hybridization. Human lymphoid cells were und to contain herpesvirus-Epstein-Barr virus. C-type cornavirus was detected in normal human and prite tissues, especially in the placenta and fibroblasts. ncogenesis may be the result of the activation or pression of oncogenic virus by cocarcinogens, utagenic factors such as radiation and chemicals, immunosuppressive factors such as malaria and viruses, cluding herpesviruses. (137 refs)

-4898 **Type D Primate Retroviruses: A Review.** (Eng) Fine, D. (Viral Oncology Program, Frederick ncer Res. Center, Frederick, MD, 21501); Schochetman, *Cancer Res* 38(10): 3123-3139; 1978.

e unique characteristics of the D-type retroviruses, their stribution in the primate population, and their relevance to man cancer are reviewed. The prototype D-type retrovirus the Mason-Pfizer monkey virus (MPMV), originally isolatfrom a breast carcinoma of a female rhesus (Old World) onkey. This is the only virus ever isolated from a primate ammary tumor, and it has in vitro transforming potential r primate cells. Viruses morphologically and immunologilly indistinguishable from MPMV have been isolated from rmal placenta and lactating mammary glands of other esus monkeys in captivity. Recently, viruses morphologilly resembling MPMV have been isolated from a langur ld World) and a squirrel (New World) monkey. Nucleic id hybridization studies indicated that the latter viruses ere endogenous in the species of origin, while MPMV apars to be a horizontally transmitted virus containing gene quences partially related to the langur monkey isolate. Stues on the immunological relatedness of the D-type reoviruses have demonstrated interspecies cross-reactivities tween the major internal and external viral proteins. Furermore, these viruses also share cross-reactivity of their mar external glycoproteins with those of the C-type baboon ndogenous virus. These interspecies reactivities can also be monstrated in natural sera from both imported and laboary-bred monkeys. Conflicting reports on the association beveen MPMV and human neoplasia are reviewed. A broad interspecies assay developed to detect immunological cross-reactivities among D-type viruses may aid in the detection of human retroviruses. (109 refs)

78-4899 **The Development of the Concept of Viral Etiology of Leukemia and Related Neoplastic Diseases. Present Status and Prospects for the Future.** (Eng) Gross, L. (Veterans Admin. Hosp., Bronx, NY, 10468). *In: Advances in Comparative Leukemia Research 1977. Proceedings of the VIIIth International Symposium on Comparative Research on Leukemia and Related Diseases, held in Amsterdam, The Netherlands on 22-26 August, 1977.* Bentvelzen, P.; Hilgers, J.; Yohn, D. S., eds. (New York: Elsevier/North Holland Biomedical Press): 503 pp.; 1-10; 1978.

The concept of a viral etiology of leukemia and related neoplastic diseases is discussed. Using C58 and AK mice, which have a high incidence of leukemia in middle age, it was demonstrated that leukemia and lymphosarcomas are caused by a filterable virus and that this virus is transmitted from one generation to another directly through the embryos. Additional experimental data indicated that leukemia, lymphosarcomas, and related neoplastic diseases are caused by transmissible oncogenic viruses in most, possibly all, animal species. In most instances, these viruses remain latent and harmless to their carrier hosts; when activated, however, they may cause fatal disease. These oncogenic viruses appear to be widely prevalent in may species, particularly within certain families, and they may be transmitted horizontally within the same generation as well as vertically from one generation to another. Both RNA and DNA viruses may be oncogenic. Leukemia and allied neoplastic diseases have fundamental features in common with "slow virus diseases" such as scrapie, kuru, and Creutzfeldt-Jakob disease, although the oncogenic viruses are much more susceptible to inactivation by heat and other factors (physical and chemical) than the agents responsible for the slow virus diseases, and they do not readily cross species. (20 refs)

78-4900 **RNA Tumor Virus Genes (Virogenes) and the Transforming Genes (Oncogenes): Genetic Transmission, Infectious Spread, and Modes of Expression.** (Eng) Todaro, G. J. (Lab. Viral Carcinogenesis, NCI, Bethesda, MD, 20014). *In: Mechanisms of Carcinogenesis. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book B), 699 pp.; 1169-1196; 1977.

The transmission of RNA tumor virus genes, the relationship between C-type RNA viruses and human neoplasia, normal functions of C-type viruses, and recombination between C-type viruses are reviewed. RNA tumor virus genes may be transmitted genetically (parent to offspring) or horizontally (animal to animal). C-type viruses, under natural conditions,

have also apparently been transferred between species that are only remotely related. In all but one case, the viral genes have become incorporated into the genome of the recipient species. The exception is the infectious primate virus group that has produced leukemias and sarcomas in primates and has been suggested to be involved in human leukemia. Several studies have indicated that this group of infectious C-type viruses, horizontally transmitted among primates, originated by transspecies infection of certain primates (gibbon, woolly monkey) by an endogenous C-type mouse virus. An infectious C-type virus closely related, if not identical, to woolly monkey virus, simian sarcoma-associated virus (SSAV), has been isolated from a cell culture derived from a woman with acute myelogenous leukemia. Endogenous primate virogenes may also be partially expressed in humans and other primates. C-type viruses may perform normal functions such as control of development, protection from infection, and transmission of genetic information. One protein that satisfies the criteria for a possible oncogene production is epidermal growth factor (EGF). Aberrant production of a growth hormone like EGF, due to introduction of sarcoma virus genes or activation of endogenous genes, may be one mechanism of transformation. (137 refs)

78-4901 **Some Ideas on the Origin of Leukemia in Man and Recent Evidence for the Presence of Type-C Viral Related Information.** (Eng) Gallo, R. C. (Lab. Tumor Cell Biology, NCI, NIH, Bethesda, MD, 20014); Saxinger, W. C.; Gallagher, R. E.; Gillespie, D. H.; Aulakh, G. S.; Wong-Staal, F.; Ruscetti, F.; Reitz, M. S. *In: Mechanisms of Carcinogenesis. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book B), 699 pp.; 1253-1285; 1977.

Evidence for the presence of C-type viral related information in patients suffering from leukemia is reviewed, and five possible mechanisms of viral leukemogenesis are presented. Intracytoplasmic viruslike particles containing high-mol-wt RNA and reverse transcriptase activity have been identified in human leukemic blood and bone marrow cells. Infectious, fully mature C-type virus, containing components related to baboon endogenous virus and simian sarcoma virus, has been isolated from a patient with acute myelogenous leukemia. Proviral sequences closely related to those of baboon endogenous virus and distantly related to those of murine leukemia virus have also been found in DNA from leukemic patients. The first model of leukemogenesis proposes a classical mechanism of infection of the stem cell by a C-type virus, resulting in complete integration of the provirus, partial expression of the virus genome, and transformation of the stem cell. In the second model, only a fragment of the provirus is integrated, but it is sufficient to cause transformation. The third model involves transformation of a regulator cell. The fourth proposes that the stem cell is infected and contains a complete provirus, but is not transformed. After a number of divisions of the stem cells, some of the progeny cells lose some or all of the provirus and adjacent cellular genes responsible for cell differentiation. These cells are blocked in normal maturation and thus have a proliferative advantage. The fifth model proposes that a C-type virus infects a target cell other than WBC. The infected cell releases DNA fragments or produces virus that secondarily infects a WBC precursor, leading to transformation. The fourth and fifth models are the most consistent with available data. (81 refs)

78-4902 **Transformation In Vitro by Adenovirus Type 2--A Model System for Studying Mechanisms of Oncogenicity.** (Eng) McDougall, J. K. (Cold Spring Harbor Lab., Cold Spring Harbor, NY, 11524); Chen, L. B.; Gallimore, P. H. *In: Mechanisms of Carcinogenesis. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book B), 699 pp.; 1013-1025; 1977.

The characteristics of rat cells transformed in vitro by adenovirustype 2 (AD2) and the in vivo behavior of these cells are reviewed. Ad2-transformed cells consistently contain a minimum segment of viral DNA representing 14% of the left-hand end of the viral genome, indicating that the transformed phenotype can be induced and maintained by this region of the viral genome. With some Ad2-transformed cell lines, immunosuppression of the newborn rat results in tumor induction, suggesting that surface antigenicity is an important factor in the in vivo growth characteristics of these cell lines. There is a correlation between a decrease in one of the surface proteins, the large, external transformation-sensitive (LETS) protein, and an increase in tumorigenicity. Oncogenicity of Ad2-transformed cells is also correlated with the amount of infectious virus used to infect the monolayer cultures in which transformed foci develop. There is evidence that cells transformed at higher multiplicities of infection retain more of the virus genome. In studies with somatic-cell hybrids, there is no indication that Ad2 sequences integrate at specific loci. Rat and hamster cells transformed by adenoviruses, simian virus 40, and herpesviruses show some similar marker chromosomes, and two of the autosomes regularly involved in rearrangements in adenovirus-transformed cells are also preferentially involved in marker formation in chemical transformants. This could suggest involvement of specific loci on the chromosomes that carry genes important in the regulation of cell growth and malignancy. (33 refs)

78-4903 **Viruses in Cancer. Evaluation of Current Evidence of Possible Role of Viruses in Human Cancer (Meeting Abstract).** (Eng) Sabin, A. B. (Medical Univ. South Carolina, Charleston, SC). *Pathology* 10(2): 187-189; 1978. (1 ref)

3-4904 Aspects of Virus Persistence and Ubiquity in Relation to Environmental and Co-Factors Meeting Abstract). (Eng) Stanley, N. F. (Dept. Microbiolo-, Univ. Western Australia, Australia). *Pathology* 10(2): 9-190; 1978. (no refs)

3-4905 Cancer, Virus Infections and the Immune Response (Meeting Abstract). (Eng) Ada, G. L. Dept. Microbiology, John Curtin Sch. Medical Res., Aus-alian National Univ., Australia). *Pathology* 10(2): 189; 78. (no refs)

3-4906 Ageing, Metabolic Immunodepression and Carcinogenesis. (Eng) Dilman, V. M. (N.N. Petrov es. Inst. Oncology, Leningrad, USSR). *Mech Ageing Dev* 3): 153-173; 1978.

ata suggesting a relationship between metabolic im-unodepression and susceptibility to neoplasia are reviewed. correlation has been suggested between increases in blood vels of free fatty acids (FFA), insulin, cholesterol, and w-density lipoproteins and immunodepressions. The same etabolic factors that inhibit cellular immunity stimulate the roliferation of somatic nonlymphoid cells, thereby increas-g the possibility of malignant transformation. States such aging, stress, pregnancy and cancer, all involving a deterio-tion of cell-mediated immunity, are characterized by a simi-r hormone-metabolic pattern. The opposing influences of e same metabolic factors on somatic, nonlymphoid cells vs lymphocytes promote the development of carcinogene-s-promoting metabolic syndrome (CPMS). Many chemical rcinogens alter the biogenic amine levels in the hypo-almus; this in turn, leads to an elevation of the hypo-alamic threshold of sensitivity to feedback control, a crease in tolerance to glucose, and an increase in blood sulin level, changes that constitute the CPMS and aging ring carcinogenesis. Thus, both normal and cancer-lated aging involve metabolic immunodepression and e CPMP due to implementation of the Law of eviation of Homeostasis during natural aging or posure to chemical carcinogens, respectively. (99 refs)

3-4907 Immunological Surveillance. (Eng) Stutman, O. (Dept. Cellular Immunobiology, Memorial oan-Kettering Cancer Center, New York, NY, 10021). *In: lechanisms of Carcinogenesis. Proceedings of the Cold Spring arbor Conferences on Cell Proliferation.* Hiatt, H. H.; Wat-n, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold pring Harbor Laboratory): Origins of Human Cancer. Vol. (Book B), 699 pp.; 729-750; 1977.

he experimental and clinical evidence that has been used to pport the immune surveillance theory is reviewed. A reflective analysis of the incidence of tumors in patients with primary and secondary immunodeficiencies does not support the generality of immunological surveillance as an operative mechanism, but does support its role in the development of lymphoreticular tumors. The clinical data from transplant patients also fail to support the orthodox view of immune surveillance. The clinical behavior of the more conventional tumors in immunodepressed transplant patients is comparable to that of tumors in nonimmunodepressed patients. The generality, efficiency, and even existence of a thymus-dependent immunosurveillance mechanism capable of destroying in situ tumors are questionable. Although a surveillancelike mechanism may be operative under certain special conditions (ie, polyoma oncogenesis and that of other DNA viruses, feline leukemia), its thymus dependency is also questionable. (79 refs.)

78-4908 World-wide Variations in Cancer Incidence as Clues to Cancer Origins. (Eng) Berg, J. W. (Dept. Preventive Medicine, Univ. Iowa, Iowa City, IA, 52242). *In: Incidence of Cancer in Humans. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4, 602 pp.; 15-19; 1977.

Generalizations are presented concerning the distribution of cancers that occur at particularly high rates (40 or more cases/yr/1,000 persons aged 35-64) in studied populations. International cancer risk patterns are reviewed briefly, as are problems associated with the pathogenesis of esophageal cancer and of other cancers (stomach, bowel, breast, and prostate). (14 refs)

78-4909 Cancer Epidemic Raises Doubts on Mineral Fibres. (Eng) McGinty, L. (No affiliation given). *New Sci* 18(1103): 428; 1978.

The results of epidemiological investigations of the cause of the high mesothelioma rate in Karain, Turkey, are reviewed. Between 1970 and 1974, almost half the people who died in Karain died of mesothelioma. It was initially thought that asbestiform fibers in the drinking water were responsible for the cancer, but recent studies suggest that fibers of volcanic silicates called zeolites are responsible. These fibers are found in the volcanic rock that the residents use for building blocks and road-making materials. Furthermore, these fibers have the same dimensions (>0.2 μm in diameter and 3-15 μm long) as the forms of asbestos (amosite, crocidolite) most active in causing mesothelioma. If the link with zeolite is confirmed, it would be the first human evidence that nonasbestos silicate fibers cause mesothelioma. Such a finding would throw doubt on the safety of manmade mineral fibers suggested as substitutes for asbestos. (1 ref.)

78-4910 **Epidemiologic Methods for Human Risk Assessment.** (Eng) Mack, T. M. (Dept. Community Medicine and Public Health, Univ. Southern California Sch. Medicine, Los Angeles, CA, 90033); Pike, M. C.; Casagrande, J. T. *In: Human Risk Assessment. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book C), 583 pp.; 1749-1763; 1977.

Three functions of the cancer epidemiologist are discussed. Analysis of population-based incidence data for the purpose of descriptive epidemiology may retrospectively confirm an association between a particular cancer and a known exposure, but it can not predict serious risks. Descriptive epidemiology, however, can identify patterns or changes in patterns of a particular cancer that could result in modifications of current hypotheses. The second function of epidemiology is to describe the association between a putative causal exposure and a disease under circumstances that permit the best possible discrimination between causal and alternative hypotheses. However, sample-size requirements may be prohibitive. The problems involved in designing an epidemiological study to test various hypotheses is illustrated by a study of endometrial cancer, which resulted in the identification of exogenous estrogens as a cause of endometrial cancer. The third function of epidemiology involves the reduction of pertinent biologic information into a comprehensible summary for the purpose of policy formulation. This function is illustrated by analysis of the risks and benefits from the addition of mammography to breast cancer screening programs. The analysis indicates that the benefits of mammograph in women under 50 are likely to come at the price of an increased risk of radiogenic breast cancer later in life. (15 refs)

78-4911 **Burkitt's Lymphoma in Tropical Countries: Epidemiology and Relationship with Malaria.** (Fre) Charmot, G. (Consultation des Maladies Tropicales, Hopital Claude-Bernard, 10, av. de la Porte d'Aubervilliers, F 75019 Paris, France); Rodhain, F.; Roze, J. M. *Nouv Presse Med* 7(4): 265-269; 1977.

Epidemiological data on Burkitt's lymphoma (BL) are reviewed, and the relationship of the tumor to malaria is discussed. BL is endemic throughout rural regions of Black Africa and New Guinea, with an incidence of 3-7/100,000 children (0-15 yr of age). Characteristically, the region has a fairly dense rural population with a low standard of living. The climate is always warm (above 18 C) and humid, conditions conducive to the permanent or prolonged transmission of malaria. Infection by Epstein-Barr virus (EBV), as determined by the level of EBV antibodies, occurs before the age of 3 yr and precedes the appearance of the tumor by 6 mo to 2-3 yr. Experiments with mice show that the malaria induced by *Paludium berghei* or *P. yoelii* facilitates the development of spontaneous or virus-induced lymphomas and the growth of BL grafts that would otherwise be rejected. In certain regions of East Africa where malaria has been controlled, the incidence of BL has decreased. It is hypothesized that a soluble mitogen produced by *P. falciparum* and found in blood of Nigerian children may have a stimulatory effect on B lymphocytes containing EBV, which may lead to growth of the lymphoma. Genetic and immunological factors may also play a role in individual susceptibility to BL. (21 refs)

78-4912 **On the Etiology and Metabolic Epidemiology of the Main Human Cancers.** (Eng) Weisburger, J. H. (Naylor Dana Inst Disease Prevention, American Health Foundation, Valhalla, NY, 10595); Cohen, L. A.; Wynder, E. L. *In: Incidence of Cancer in Humans. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4, 602 pp.; 567-602; 1977.

Concepts maintaining that the etiologies of the main human cancers stem largely from human life-styles are reviewed. Most cancers of the respiratory tract are due to excessive smoking, as are cancers of the pancreas, kidneys, and bladder. Prevention of these diseases hinges on education of the public and collaboration of industry and government to produce and give preferential marketing to lower tar cigarettes. Cancers of the breast, prostate, ovary, endometrium, and colon are associated with a high fat content in the diet. Cancer of the pancreas is also associated in part with diet. Prevention of these cancers hinges on lowering fat consumption from the prevailing level of 45% of the caloric intake to 25%-33%. This would be aided by cooperation of industry with agricultural and governmental agencies to produce and market foodstuffs that would permit the consumer to adopt the lower fat diet more readily or automatically. Cancer of the stomach might be prevented by increasing the consumption of vitamin C, low-temperature food storage to prevent nitrite formation, and controlling the use of nitrite as a preservative. (155 refs)

78-4913 **The Malignant Lymphomas: Epidemiology and Related Aspects.** (Eng) Vianna, N. J. (Bureau Occupational Health and Chronic Diseases and Lymphoma Studies, Cancer Control Bureau, Dept. Health, Albany, NY). *Pathobiol Annu* 7: 231-255; 1977.

Three issues of importance to malignant lymphoma are reviewed: the heterogeneity between and within many of the lymphoma groups, the probable importance of environmental and genetic factors in the pathogenesis of malignant lymphoma, and evidence suggesting that an infectious agent might have an etiological role in certain disorders (Hodgkin's disease and Burkitt's lymphoma). (193 refs.)

78-4914 **Epidemiology of Esophageal Carcinoma (Letter to Editor).** (Eng) Mizroch, S. (Kaiser Foundation Hosp., San Francisco, CA). *JAMA* 239(22): 2340-2341; 1978.

ge (older), sex (male), race (nonwhite), and geography exert ıbstantial influence on the increased incidence of esophageal ırcinoma. Cigarette smoking, alcohol consumption, and ıermal irritation from imbibing hot foods are also predispos- ıg factors. There are links between carcinoma and various ypes of obstructive esophageal lesions. An increased inci- ence of carcinoma in achalasia, Barrett's esophagus, lye rictures, and Plummer-Vinson syndrome should encourage ıe high index of suspicion incumbent to early diagnosis. (4 efs)

8-4915 **The Occurrence of Oesophageal Cancer - A World-wide Survey (Meeting Abstract).** (Eng) luir, C. S. (International Agency Res. on Cancer, 150, ours Albert Thomas, 69372 Lyon Cedex 2, France); Nec- oux, J. *In: Third International Symposium on Oncology Held v Taj Pahlavi Cancer Institute in Tehran, 4-8 March, 1978.* aj Pahlavi Cancer Institute, Pahlavi Medical School, Teh- n University. (Tehran, Iran): 115 pp.; 103-104; 1978. (no efs)

8-4916 **Pulmonary Tuberculosis and Bronchial Carcinoma (2 Letters to Editor).** (Eng) Healy, T. M. Dept. Pathology, Univ. Coll., Dublin 2, Ireland); MacGre- or, G. A. *Lancet* 2(8085): 372; 1978.

he use of the word "opportunist" as applied to tuberculosis omplicating bronchial carcinoma can be validated by a re- iew of the literature. However, in another opinion, it is stat- d that the association may be more than fortuitous. Since ıycobacterial infections appear to be more common in can- er patients than in the general population, it is suggested that ıe chronic immune irritation generated by tuberculosis and ırcoidosis is an initiating factor in bronchial carcinoma. (11 efs.)

8-4917 **Changing Patterns of Cancer in Japan with Special Reference to the Decrease in Stomach Cancer Mortality.** (Eng) Hirayama, T. (Epidemiology Div., Natl. ancer Center Res. Inst., Tsukiji 5, Chuo-ku, Tokyo, Japan). *n: Incidence of Cancer in Humans. Proceedings of the Cold oring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Vatson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold oring Harbor Laboratory): Origins of Human Cancer. Vol. 602 pp.; 55-75; 1977.

he steady downward trend in age-specific death rates for omach cancer in Japan is discussed. Almost no increase in ıortality for cancer of all sites was observed in men during ıe last decade and a slight decrease was observed among omen. The greatest decreases occurred in cervical cancer ates and in the rates of stomach cancer in both men and omen. Sharp increases were observed for leukemia and for ancer of the lung, pancreas, prostate, urinary tract, co- n-rectum, liver, breast, and ovary. The risk of stomach can- er was significantly increased in daily cigarette smokers and significantly reduced in those who ate green-yellow vegetables daily and those who drank two glasses of milk daily. The decline in stomach cancer mortality appears to be due to dietary improvements and to the effect of early detection. The mortality rate for colon cancer and the colon cancer-rectal cancer ratio were highest in persons who consumed a small amount of rice daily and in daily beer drinkers. Increases in the breast cancer mortality rate may be due to a decline in the birth rate or to the rapidly increasing intake of dietary fat. Mortality from breast cancer was highly correlated with pork intake and, to a lesser extent, with animal fat intake. Daily cigarette smoking was the most important cause of lung cancer. Causes for changing patterns in the rates of other cancers are also discussed. (13 refs.)

78-4918 **The Origin of Malignant Tumors of the Upper-Airways, the Digestive Tract and the Ear. Organ-Resistance and Organ-Disposition (Organotropy) by the Origin of Malignant Primary Tumors.** (Ger) Leicher, H. (Langenbechs. 1, 6500, Univ.-HNO-Klinik, Mainz, W. Germany). *Laryngol Rhinol Otol (Stuttg)* 57(3): 162-176; 1978.

General biological mechanisms in the genesis of malignant tumors of the upper respiratory and digestive tracts and of the ear are reviewed. Carcinomas of the nose, trachea, mouth, esophagus, and middle ear are significantly less frequent than those of the bronchi and larynx, a finding that cannot be explained by differences in the degree of exposure of these organs to carcinogenic substances. It can be explained by differences in their resistance to malignant transformation and in their disposition (organotropy). Variations in resistance and disposition are due to differences in cell regeneration rate, ability to repair nucleic acids; concentration of tissue-specific proteins (chalones) that inhibit cell proliferation and tumor growth, increase in metabolism before and during malignant transformation, nonspecific mesenchymal reaction, immune response to tumor cells, and affinity of tissues to chemical carcinogens. In most cases, there is a positive correlation between the cell regeneration rate and the occurrence of malignant epithelial tumors. The low incidence of malignant tumors of the gingiva, floor of the mouth, tongue, and buccal mucosa, in spite of the high cell regeneration rate in these tissues, is due to the steady release of large numbers of granulocytes from the gingiva. (83 refs)

78-4919 **The Role of Unsaturated Bile Acids in the Etiology of Large Bowel Cancer.** (Eng) Hill, M. J. (Central Public Health Lab., London NW9 5DX, England). *In: Human Risk Assessment. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book C), 583 pp.; 1627-1640; 1977.

The role of bile acids in large bowel cancer is reviewed. When populations in countries having different rates of large bowel cancer or populations in the same country but from different

socioeconomic levels were compared, the risk of large bowel cancer was found to correlate with the concentration of bile acids. The bile acids were more extensively degraded in stools from high-incidence populations than in those from groups with a lower incidence. The hypothesis that certain clostridia (referred to as NDC) are able to dehydrogenate the bile acid nucleus to produce unsaturated bile acids and that the combination of high concentrations of bile acid substrate and of NDC confers a high risk of colon cancer was tested and confirmed in a case-comparison study. A high fecal bile acid concentration alone characterized 83% of the large bowel cancer patients compared with only 19% of the comparison patients. Of the four combinations of fecal bile acid concentration and presence or absence of NDC, the combination of high fecal bile acids and NDC conferred the highest risk. Other studies have indicated that the number of organisms in stools producing cholanoyl 7α-dehydroxylase is correlated with the incidence of large bowel cancer and that 3-oxochola-4,6-dien-24-oic acid is the key etiological agent. (42 refs)

78-4920 **Experimental Approaches to Benign Prostatic Hyperplasia.** (Ger) Jacobi, G. H. (Urologische Universitatsklinik, Langenbeckstrasse 1, 6500 Mainz, W. Germany). *Aktuel Urol* 9(2): 73-80; 1978.

The normal and pathologic growth of the prostate gland is stimulated by testicular hormones. The concentration of dihydrotestosterone, the principal androgen in androgenic target tissues, is increased in benign prostatic hypertrophy (BPH) as a result of pathologic growth. The decrease in Leydig cell function with advancing age results in quantitative changes of the peripheral hormone pool (decrease in free testosterone, testosterone glucuronide dihydrotestosterone, and adrenal androgen level, and increase in testosterone-binding globulin and estradiol levels and in estradiol/testosterone and testosterone/dihydrotestosterone ratios). Thus, qualitative intracellular hormone alterations are most likely to be responsible for the development of BPH. Prostatic hypertrophy occurs in only two species, man and dog, which suggests the use of the latter as a model for this condition. Androstanediol induces unregulated adenomatous growth of the prostate in the dog. This hormone is a normal product of testicular secretion and prostatic metabolism. The increased formation of androstanediol in the prostate is paralleled by an increased growth of the gland. Cellular androstanediol synthesis is increased significantly in men with prostatic adenomas, compared with normal men. The findings suggest the direct role of androstanediol in the pathogenesis of BPH. (50 refs)

78-4921 **Results of Research on Precancerous Changes in the Endometrium.** (Rus) Zheleznov, B. I. (Moscow, USSR). *Akush Ginekol (Mosk)* (3): 10-17; 1978.

According to this review article, "precancer of the endometrium" (PCE) should include atypical hyperplasia of the functional and/or basal layer of the endometrium, focal adenomatosis in glandular and basal hyperplasia, polyps, and adenomatous endometrial polyps. During the last 16 yr, PCE was diagnosed in 202 patients, other forms of hyperplasia in 1,006, and endometrial polyps in 2,031. Malignant transformation of atypical hyperplasia and focal adenomatosis was observed in 25/202 PCE patients. (no refs)

78-4922 **Comparison of Neoplastic Hepatic Lesions in Man and Experimental Animals.** (Eng) Popper, H. (Stratton Lab. Study of Liver Diseases, Mount Sinai Sch. Medicine, City Univ. New York, New York, NY, 10029); Maltoni, C.; Squire, R. A.; Thomas, L. B. *In: Human Risk Assessment. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book C), 583 pp.; 1359-1382; 1977.

The induction of hepatic tumors in animals and clinical observations of hepatic tumors in humans are compared. The progression from fibrotic lesions to angiosarcoma in man following exposure to vinyl chloride (VC), inorganic arsenicals, and Thorotrast is almost identical to changes observed in rodents treated with VC. This similarity in the evolution of hepatic lesions supports the predictive nature of animal experimental studies for human carcinogenesis. The major difference between the species was the greater fibroblastic reaction in man. The development of hepatocellular carcinoma in human and rodent nodules supports the concept of multiple cell populations in hepatocarcinogenesis. In the VC-associated lesions, the simultaneous proliferation of hepatocytes and sinusoidal cells, the latter potentially terminating in angiosarcoma, is stressed. The metabolic processes underlying this evolution remain to be established. (77 refs.)

78-4923 **Tumor Heterogeneity and the Biology of Cancer Invasion and Metastasis.** (Eng) Fidler, I. J. (Cancer Biology Program, NCI Frederick Cancer Res. Center, Frederick, MD, 21501). *Cancer Res* 38(9): 2651-2660; 1978.

The spread of tumor tissue through the lymphatic and hematogenous compartments of the circulatory system is discussed on the basis of experiments with the B16 melanoma in C57BL/6 mice. The development of a metastasis is dependent on an interplay between host factors and the intrinsic characteristics of malignant tumor cells. The process of metastasis is highly selective, and the metastatic lesion represents the end point of many destructive events that only a few cells can survive. Neoplasms, which are predominantly heterogeneous in nature, contain a variety of subpopulations of cells with differing metastatic potential. Furthermore, metastatic cell variants have been shown to preexist in murine neoplasms of old and recent origin. The possible existence of highly metastatic variant cells within a primary tumor suggests that

neoplasm should no longer be considered a uniform entity. he design of effective therapeutic agents should be directed ward the few but lethal metastatic subpopulations of cells. 3 refs.)

3-4924 **Progression and Genesis of Human Tumors** (Ita) Prodi, G. (Istituto Cancerologia, Bologna, aly). *Recent Prog Med (Roma)* 63(6): 669-687; 1977.

udies of the monoclonal nature of tumors and their preneolastic stages, growth, differentiation and progression are reiewed. Tumor progression is irreversible, discontinuous, fol, and, in each individual case, unpredictable. (5 refs)

8-4925 **Introduction.** (Eng) Doll, R. (Univ. Oxford, Oxford OX2 6PS, England). *In: Incidence of Cancer in Humans. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4, 602 pp.; 1-12; 1977.

The main clues to the origin of cancer that have been provided by epidemiological studies are reviewed. Included in the discussion are environmental agents, industrial pollution, diet, the interaction of agents, viruses, systemic factors, and genetic factors. (25 refs)

78-4926 **Genetic Predisposition to Cancer.** (Eng) Knudson, A. G. (Medical Genetics Center, Graduate Sch. Biomedical Sciences, Univ. Texas Health Science Center, Houston, TX, 77030). *In: Incidence of Cancer in Humans. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4, 602 pp.; 45-52; 1977.

In a review of the role of heredity and environment in the development of cancer, four groups of individuals can be recognized. The first group has a genetic predisposition to cancer even in the absence of environmental variation. The second group has a predisposition imposed by environmental variation in the absence of genetic variation. The third has a predisposition imposed by both genetic and environmental factors. The fourth group has neither a genetic nor environmental predisposition. Group 1, hereditary cancers, comprises only 1%-2% of all cancers but may comprise a large percentage of a particular cancer (eg, 40% for retinoblastoma). Several multiple mutation models have been proposed to explain these cancers, and most propose that there is an initial germinal mutation followed by a somatic mutation. In some cancers (ie, epithelial carcinomas of adulthood), a third event, perhaps a chromosome abnormality, may be required for the development of malignancy. The predisposition in the third group is represented by conditions such as xeroderma pigmentosum and ataxia telangiectasia. Cancers of the second and third groups make up 70%-80% of all cancers in industrialized nations. The fourth group, comprising approx 25% of the total cancer incidence, results from spontaneous or background somatic mutations and represents the nonpreventable cancers for which diagnosis and therapy will always be important. (35 refs)

78-4927 **Genetic Regulation of Susceptibility to Polycyclic-hydrocarbon-induced Tumors in the Mouse.** (Eng) Kouri, R. E. (Dept. Biochemical Oncology, Microbiological Associates, Bethesda, MD, 20016); Nebert, D. W. *In: Mechanisms of Carcinogenesis. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book B), 699 pp.; 811-835; 1977.

The membrane-bound monooxygenase systems are reviewed, and the relationship between the murine aryl hydrocarbon (*Ah*) locus and increased susceptibility to chemical tumorigenesis, drug toxicity, and mutagenesis is discussed. A single allelic difference or a very small number of genes may have a profound influence on an individual's increased susceptibility to chemical carcinogenesis, drug toxicity, and congenital malformations. However, genes other than the *Ah* locus appear to influence an individual's risk for tumorigenesis. DNA repair, viral expression, and immunological tolerance may also be modifying factors in tumorigenesis. The interplay between the *Ah* locus and these factors, as well as the role of the factors themselves, in susceptibility to cancer can be determined hypothetically using an experimental approach outlined. (69 refs.)

78-4928 **Hereditary Factors in Human Cancer.** (Eng) Kellermann, G. (Dept. Human Oncology, Univ. Wisconsin, Madison, WI, 53706). *In: Mechanisms of Carcinogenesis. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book B), 699 pp.; 837-845; 1977.

The influence of genetic factors on human cancer is discussed. Epidemiologic data can be used to determine whether genetic factors are involved in certain common cancers. These data suggest that as much as 80% of all human cancers have some environmental element as their critical etiologic factor, but that the susceptibility to a particular cancer is inherited. Thus, the majority of carcinogens may be so-called precarcinogens that require enzymatic transformation to become real carcinogens. Interindividual variation of some of the activating enzymes might explain why some individuals are sensitive or resistant to the action of environmental carcinogens. For example, in vivo and in vitro studies demonstrate that the human population can be divided into slow and fast metabolizers of certain drugs and of the carcinogen

benzo(a)pyrene. Such studies have indicated that heavy smokers with a genetically high aryl hydrocarbon hydroxylase (AHH) activity are at greater risk for developing lung cancer than heavy smokers with low AHH activity, because the former produce more of the carcinogenic epoxides than the latter. A genetically high AHH activity may also be a factor in the etiology of laryngeal cancer. (22 refs.)

78-4929 **Constitutional and Hereditary Factors in the Genesis of Human Tumors.** (Ita) Prodi, G. (Istituto Cancerologia, Bologna, Italy); Grilli, S. *Recent Prog Med (Roma)* 63(6): 622-640; 1977.

Studies of hereditary human tumors are reviewed. Nephroblastoma, retinoblastoma, neuroblastoma, neurofibromatosis, pheochromocytoma, colonic polyposis, and hereditary adenocarcinomatosis are the principal hereditary tumors. (37 refs)

78-4930 **Prenatal Factors.** (Eng) Miller, R. W. (Clinical Epidemiology Branch, NCI, NIH, Bethesda, MD, 20014). *In: Incidence of Cancer in Humans. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4, 602 pp.; 381-388; 1977.

The association between human cancer and congenital malformations is discussed. Included in the discussion are xeroderma pigmentosum and ataxia telangiectasia, hereditary retinoblastoma with osteosarcoma, common features in persons at high risk of specific cancers, environmental causes of cancers and malformations, and the overlap at mutagenesis, carcinogenesis, and teratogenesis. (52 refs)

78-4931 **Chromosomal Abnormalities in Human Neoplasia.** (Ger) Bartram, C. R. (I. Medizinische Klinik, Universitat Hamburg, Martinistrasse 52, D-2000 Hamburg 20, W. Germany); Rudiger, H. W. *Klin Wochenschr* 56(15): 733-741; 1978.

Current knowledge on the association between chromosome aberrations and malignant tumors is reviewed. Specific topics covered include cancer-prone chromosome abnormalities, chromosome abnormalities related to tumors, and chromosome abnormalities related to carcinogens. Observations in humans are discussed in connection with in vitro experimental data. (92 refs.)

78-4932 **Cellular Transformation and the 'Morphologic Phenotype' of Transformed Cells.** (Eng) Pastan, I. (NCI, Bethesda, MD, 20014); Willingham, M. *Nature* 274(5672): 645-650; 1978.

Changes in the adhesion, appearance, and surface properties of cells undergoing transformation are reviewed, with emphasis on the role of cyclic AMP (cAMP) and cell-surface protein (CSP) in this process. In most cases, these changes are linked to a diminished adhesion of the cell to the substratum. Treatment of transformed cells with cAMP has been reported to induce the flattened appearance characteristic of normal fibroblastic cells, increase their adhesion to a substratum, decrease their agglutinability by plant lectins, decrease the number of surface microvilli, and decrease growth rate; but it does not restore contact inhibition of growth. However, not all transformed cells respond to cAMP. The response of the parental untransformed cell usually indicates whether the transformed derivative will respond to cAMP. cAMP levels are reduced and adenylate cyclase levels are altered in some transformed cells. CSP is decreased in many types of transformed cells. In Rous sarcoma virus-transformed chick embryo cells, the decrease is primarily due to a decrease in the rate of synthesis of CSP, and it is accompanied by a reduction in the amount of translatable messenger RNA for CSP. The addition of highly purified CSP to cultures of transformed cells increased cell-substratum adhesion and produced cell elongation, but it did not restore growth control. Expression of the product of the transforming (*src*) gene of RNA tumor viruses promotes growth and usually produces the morphologic phenotype of transformation in cultured fibroblasts. The changes closely resemble those that occur when quiescent cells are stimulated to grow by addition of an appropriate peptide hormone, such as insulin. (82 refs.)

78-4933 **Control of Normal Cell Differentiation and the Phenotopic Reversion of Malignancy in Myeloid Leukaemia.** (Eng) Sachs, L. (Dept. Genetics, Weizmann Inst. Science, Rehovot, Israel). *Nature* 274(5671): 535-539; 1978.

Cultured myeloid cells can be used to determine and dissect the controls that regulate the growth and differentiation of macrophages (M) and granulocytes (G) and the development of myeloid leukemia. Normal myeloid precursors can be induced to grow and differentiate to mature M and G by a protein M and G inducer (MGI) that is secreted by various types of cells, including fibroblasts and macrophages. One type of myeloid leukemia cell in both humans and mice can be induced to differentiate normally by MGI. In mice, this differentiation has also been demonstrated in vivo. This type of leukemia (MGI+D+, D+ for differentiation to mature cells) from different strains of mouse has been cloned in culture. Mature cells induced from MGI+D+ are no longer malignant in vivo and no longer multiply in vitro. MGI+D+ are viable and can grow in the absence of MGI, whereas normal cells require MGI for viability and growth. It is proposed that an inadequate supply of MGI can occur in vivo, possibly because of a decrease in MGI synthesis or the production of MGI inhibitors, that would limit the growth of normal cells without affecting the growth of leukemic cells. MGI+D+ cells do not have a normal diploid

karyotype, and the change in requirement for MGI for cell viability and growth was associated with a chromosome abnormality both in vitro and in vivo, suggesting that the origin of leukemia due to loss in requirement for MGI for viability and growth is genetic and due to a chromosomal change. Cell competence for induction of normal differentiation by MGI was associated with certain membrane qualities and also with the production and inducibility of C-type RNA virus. It is suggested that the mouse chromosomes (2 and 12) carrying the genes that control cell competence also carry genes that control the malignancy of the cells. (84 refs.)

78-4934 **Incidence of Cancer in Population with Exceptional Exposure to Metals.** (Eng) Hernberg, S. (Dept. Epidemiology and Biometry, Inst. Occupational Health, Helsinki 29, Finland). *In: Incidence of Cancer in Humans. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4, 602 pp.; 147-157; 1977.

Experimental and human epidemiologic data on the carcinogenicity of arsenic, beryllium, cadmium, chromium, iron, nickel, and lead are reviewed. As causes skin cancer in humans and likely induces lung cancer as well. Lymphatic cancers and hemangiosarcoma of the liver also appear to be connected with As exposure. Experimental data indicate that iv Be salts cause osteogenic sarcomas in rabbits and mice and Be aerosols cause pulmonary cancer in rats and monkeys. Epidemiological studies of humans, however, are inconclusive. Cd appears to increase the risk of prostate, renal, and respiratory cancer in humans but more studies are necessary before studies are necessary before definite conclusions can be drawn. Studies with hexavalent Cr have shown an excess of respiratory cancer in chromate workers, but the exact identity of the compound or compounds responsible for the carcinogenesis is unknown. Furthermore, there are no conclusive negative epidemiologic studies of workers exposed to trivalent chromium. Data on the carcinogenicity of Fe in humans is inconclusive, even though Fe-polysaccharide complexes have induced local sarcomas in experimental animals. There is strong epidemiologic evidence supporting the carcinogenicity of Ni compounds, but the exact identity of the compounds involved is not certain. Studies of the carcinogenicity of Pb have not shown any positive results. (89 refs)

78-4935 **Effects of Urethane Administration on the Sedimentation Patterns of Mouse and Rat Liver DNA in Alkaline Sucrose Gradients.** (Eng) Floot, B. G. (Chemical Carcinogenesis Div., Antoni van Leeuwenhoek-Huis, Netherlands Cancer Inst., Amsterdam, Netherlands); Philippus, E. J.; Scherer, E.; Den Engelse, L. *Chem Biol Interact* 21(2/3): 331-336; 1978.

The effect of urethane on the alkaline sucrose sedimentation pattern of mouse and rat liver DNA was determined. C3Hf/A male mice and Sprague-Dawley female rats were two-thirds hepatectomized and treated 3 wk later (24 hr before sacrifice) with 1 mg/g urethane ip. No significant changes in the DNA sedimentation pattern were observed. Thus, the reported formation of alkali-labile ethyl phosphotriesters in DNA by urethane is at most a minor process of alkylation. (10 refs.)

78-4936 **Significance of Repair of Human DNA: Evidence from Studies of Xeroderma Pigmentosum.** (Eng) Robbins, J. H. (Dermatology Branch, NCI, NIH, Public Health Service, US Dept. Health, Education, and Welfare, Bethesda, MD, 20014). *J Natl Cancer Inst* 61(3): 645-656; 1978.

Recent studies relating certain clinical manifestations of xeroderma pigmentosum (XP) to the patient's defective DNA repair are reviewed. XP patients develop excessive freckling on sun-exposed skin at an early age (usually before 2 yr) and this frequently leads to tumor development. The tumors occur at the same frequency as, and are indistinguishable from, tumors in patients without XP, but XP patients can develop hundreds of these tumors by the age of 30. Cultured dermal fibroblasts from all excision repair-deficient XP cells show a reduced rate of UV-induced unscheduled DNA synthesis. Furthermore, an increased frequency of UV-induced sister chromatid exchanges exists in these cells, possibly as a result of unrepaired DNA damage. The primary inherited DNA repair defect has not been established in any form of XP. Neurologic damage accompanying XP appears to be the result of UV-induced DNA damage. It is hypothesized that UV radiation-induced damage in XP cells requires the same process(es) for repair as the currently unknown damage postulated to occur in the DNA of the CNS of XP and normal individuals during embryonic and postnatal life. The XP neurons are not repaired as efficiently as normal neurons and, although the neuronal DNA does not replicate after the second postnatal year, proper functioning of this DNA is necessary for neuron survival. Cell death eventually results from the UV-induced damage. The acute sun sensitivity of some XP patients appears to be the result of excessive killing or damage of skin cells as a result of inadequate DNA repair. An analysis of the various XP complementation groups and of the biochemical and physicochemical abnormalities in XP cells is also presented. (120 refs)

78-4937 **Role of Cyclic Adenosine-3,5-monophosphate in Tumorigenesis.** (Rus) Simkhovich, B. Z. (Inst. Organic Synthesis, Riga, USSR); Lidak, M. Iu.; Gilev, A. P. *Khim Farm Zh* 12(6): 17-31; 1978.

Literature on the role of cyclic AMP (cAMP) in cell metabolism and differentiation is reviewed with special attention to alterations in the cAMP system during tumorigenesis. The characteristic feature of a series of malignant tumors was an extremely low level of cAMP. The cAMP concentration was also decreased after exposure of tissue to carcinogens. Recent studies show that cAMP can inhibit tumor growth. (142 refs.)

78-4938 **Carcinogenicity and Bacterial Mutagenicity of 47 Structurally Related Heterocyclic Compounds (Meeting Abstract).** (Eng) Schwind, H. (Pharmakologisches Institut der Universitat, D-6500 Mainz, W. Germany); Oesch, F.; Zajdela, F.; Jacquignon, P.; Croisy, A.; Perin, F.; Glatt, H. *Experientia* 34(7): 918; 1978. (no refs)

78-4939 **Sensitivity to Five Mutagens in Fanconi's Anemia as Measured by the Micronucleus Method.** (Eng) Heddle, J. A. (Dept. Natural Science, York Univ., Toronto, Ontario M3J 1P3, Canada); Lue, C. B.; Saunders, E. F.; Benz, R. D. *Cancer Res* 38(9): 2983-2988; 1978.

The micronucleus technique was used to measure the sensitivity of Fanconi's anemia (FA) patients to mitomycin C (MMC), ethyl methanesulfonate, methyl methanesulfonate, x-rays, and 5-bromodeoxyuridine. Blood samples from four groups of patients were cultured: 4 patients with FA, 1 patient with aplastic anemia of uncertain etiology, 6 carriers of the FA gene (parents of the patients), and 6 normal controls. MMC treatment of cultures from the FA patients resulted in an increase in micronuclei formation that was readily distinguishable from the response of the other groups. This corresponded to a tenfold increased sensitivity to chromosomal breakage by the cross-linking agent. The micronucleus technique was also successful at detecting the increased spontaneous rate of chromosome breakage in FA. None of the other groups differed significantly in response to MMC or to the other mutagens. FA cells were no more sensitive to the other agents than were cells of normal controls, except for a 50% increase in sensitivity to x-rays. These findings indicate that the micronucleus technique can be used to diagnose cases of FA and to extend the information available on the sensitivity of various genotypes to chromosomal damage by various agents. (32 refs.)

78-4940 **Mammalian Cell Transformation In Vitro.** (Eng) Styles, J. A. (Imperial Chemical Industries Ltd., Central Toxicology Lab., Alderley Park, Cheshire, England). *Br J Cancer* 37(6): 931-936; 1978.

The use of in vitro transformation as a rapid test to detect carcinogenic chemicals was evaluated. WI-38 (human lung), Chang (human liver), and BHK-21 (baby Syrian hamster kidney) cells were used to test 120 organic chemicals. The assay was 94% accurate in determining carcinogenic activity using two cell lines. The predictive figure was only slightly reduced when one cell type was used (88% for WI-38 and Chang, and 91% for BHK-21). Only 11 compounds were detected with the use of one cell type. Thus, species or organ of origin of the tester cells is of no significance in this assay, and one cell type offers no great predictive advantage over another. Comparison of the data revealed that 106 compounds were correctly identified by both the mammalian cell transformation and bacterial-mutation tests. Of the remaining 14 compounds, 7 were correctly identified only by the transformation test and 5 were identified only by the bacterial-mutation test. Few carcinogens transformed the human cells without auxiliary metabolism by a rat liver homogenate. (40 refs)

78-4941 **The Usefulness of Mutagenicity Tests as Prescreening Cancer Tests: Comparing "Host-Mediated Assay" and "Mammalian Spot Test".** (Ger) Fahrig, R. (Freiburg, W. Germany). *Staub-Reinhalt Luft* 38(6): 232-235; 1978.

The usefulness of two mutagenicity test systems for prescreening chemical carcinogens was compared: (1) the host-mediated assay (yeast/rat) for detecting the organospecificity of carcinogens and (2) the in vivo mammalian spot test for detecting genetic alterations, especially point mutations in murine somatic cells. Parallel testing of carcinogens demonstrated that the spot test was not only capable of identifying carcinogens and their target organs, but also required a lower carcinogen dose than the host-mediated assay. In the host-mediated assay, yeast cells were injected into rat testicles and tail veins. Within min, the tail-vein injected yeast cells were filtered from the blood and transported to organs such as the liver, lungs, and spleen. Subsequently, the yeast cells were retrieved from testicles, liver, and lungs and examined for genetic alterations. Of the 15 mutagens or carcinogens tested, 6 were most active in the lungs and 9 in the liver. Six mutagens did not appear in the testicles and 2 did not appear in either the testicles or liver. Not all mutagens reacted in this assay, but in the spot test, all compounds reacted, even those that induced genetic mutations exclusively. (45 refs.)

78-4942 **Carcinogenic Activity of *Symphytum officinale*.** (Eng) Hirono, I. (Dept. Carcinogenesis and Cancer Susceptibility, Inst. Medical Science, Univ. Tokyo, Shirokanedai, Minato-ku, Tokyo 108, Japan); Mori, H.; Haga, M. *J Natl Cancer Inst* 61(3): 865-869; 1978.

he carcinogenicity of *Symphytum officinale* L., or Russian omfrey, which is used as a green vegetable or a tonic in apan, was studied in inbred ACI rats. Three groups of 19-28 ats were fed comfrey leaves (8%, 16%, or 33% of diet) for 80-600 days; four additional groups of 15-24 rats were fed omfrey roots (0.5%-8% of diet) for varying lengths of time. control group was given a normal diet. Hepatocellular denomas were induced in all experimental groups that reeived the diets containing comfrey roots and leaves. Tumor ncidence ranged from 4% (group fed leaves at 8% of diet or 600 days) to 86.3% (group fed roots at 8% of diet until eath). Hemangioendothelial sarcomas of the liver were also nduced at a low incidence. The results show that comfrey oots were much more toxic than the leaves. They strongly uggest that the pathologic changes in the liver were induced y the pyrrolizidine alkaloids present in comfrey. (13 refs.)

8-4943 **The Implant Test.** (Eng) Longstaff, E. (No affiliation given). *Br J Cancer* 37(6): 954-958; 978.

technique is described whereby the histological changes bservable after the sc implantation of filter disks containing test material are used to predict the carcinogenic potential f the material. An irritant (a Millipore filter of specific pore ize) was included in the implant, and the test compound was uspended in gelatin to induce the production of proteolytic nzymes. The disks were implanted into the dorsolumbar reion of 2-mo-old Alderley Park Swiss mice. Control implants ontained dimethyl sulfoxide but no added test material. The arcinogenic potential of 76/111 compounds was predicted orrectly. Only 19/52 carcinogens were positively identified, ut there were only 2 false-positive results among the 59 nonarcinogenic compounds tested (3% false-positive rate). Beause the implant test proved insensitive and required a proracted duration of study for little return, it would be nadequate as a routine test for identifying new carcinogens. Iowever, it shows promise as a model for the regular producion of sc sarcomas and carcinomas. (8 refs)

8-4944 **Use of the Fluctuation Test to Detect Genetic Activity of Environmental Chemicals in *Aspergillus Nidulans* (Meeting Abstract).** (Eng) Kappas, A. (Dept. Biology, Nuclear Res. Center, Democritus, Athens, Greece); Demopoulos, N. *Mutat Res* 53(2): 208; 1978. (1 ref)

8-4945 **Intravenous Host-mediated Assay for Detection of Mutagenesis with *Saccharomyces cerevisiae* (Meeting Abstract).** (Eng) Frezza, D. (Lab. Environmental Mutagenesis, NIEHS, Research Triangle Park, NC, 27709); Zeiger, E. *Environ Health Perspect* 20: 235; 1977. (no refs)

78-4946 **Description and Calibration of a Forward Mutation System in Salmonella (Meeting Abstract).** (Eng) Pueyo, C. (Lab. Environmental Mutagenesis, NIEHS, Research Triangle Park, NC, 27709). *Environ Health Perspect* 20: 235; 1977. (no refs)

78-4947 **Effect of Excision Repair-Deficient Mutation *uvs*-2 on the Mutagenic and Killing Activities of 7 Chemical Mutagens in Heterokaryons of *Neurospora crassa* (Meeting Abstract).** (Eng) Brockman, H. E. (Illinois State Univ., Normal, IL, 61561); Hung, C. Y.; Ong, T. M.; de Serres, F. J. *Mutat Res* 53(2): 156-157; 1978. (3 refs)

78-4948 **Chemical Mutagenesis in UV-sensitive Strains of *Neurospora crassa* (Meeting Abstract).** (Eng) Inoue, H. (NIEHS, Research Triangle Park, NC, 27709); Ong, T. M.; De Serres, F. J. *Environ Health Perspect* 20: 235; 1977. (no refs)

78-4949 **Test for Repair Replication of DNA In Vivo in Liver of Animals Treated with Carcinogens (Meeting Abstract).** (Eng) Craddock, V. M. (MRC Toxicology Unit, Woodmansterne Road, Carshalton, Surrey, England). *Br J Cancer* 38(1): 170; 1978. (1 ref)

78-4950 **The Effect of Bacterial Plasmids on Mutagenesis (Meeting Abstract).** (Eng) Monti-Bragadin, C. (Inst. Microbiology, Univ. Trieste, Trieste, Italy); Babudri, C. N.; Tamaro, M.; Cinco, M.; Molina, A. M. *Mutat Res* 53(2): 231-232; 1978. (no refs)

78-4951 **Mutation Induction by Indirectly Acting Mutagens in Drosophila Larvae (Meeting Abstract).** (Eng) Kortselius, M. J. (Dept. Radiation Genetics and Chemical Mutagenesis, State Univ. Leiden, Leiden, Netherlands); Vogel, E. *Mutat Res* 53(2): 212; 1978. (no refs)

78-4952 **Mutagenicity of Intestinal Bacteria.** (Eng) Suzuki, K. (Inst. Physical and Chemical Res., Wako-shi, Saitama 351, Japan); Mitsuoka, T. *Mutat Res* 50(2): 295-299; 1978.

The mutagenicity of 45 intestinal bacterial strains was tested by the rec-assay, which measures the lethal effects on a recombination-deficient *Bacillus subtilis* strain (M45 *rec*-). Of the 16 strains that showed lethal activity, 8 were Bifidobacteria strains. Positive strains that are predominant species in

the human intestine included *Bifidobacterium adolescentis, Bifidobacterium infantis, Bifidobacterium longum, Bacteroides fragilis ss. fragilis, Bacteroides multiacidus,* and *Eubacterium aerofaciens. Bacteroides multiacidus, Peptostreptococcus parvulus, Streptococcus faecium,* and *Veillonella parvula* were mutagenic for *Salmonella typhimurium* strain TA1535, indicating that they induce base-pair substitution mutations. (13 refs)

78-4953 **Mutagenicity Tests with Styrene Oxide in Mammals.** (Eng) Fabry, L. (Mammalian Genetics Lab., Dept. Radiobiology, CEN-SCK, B-2400 Mol, Belgium); Leonard, A.; Roberfroid, M. *Mutat Res* 51(3): 377-381; 1978.

The capability of styrene oxide to induce chromosomal damage was determined using four mammalian test systems in vivo and one in vitro. Adult male BALB/c mice were given a single ip injection of 250 mg/kg styrene oxide, and the induction of chromosomal aberrations in the bone marrow cells, the production of micronuclei in polychromatic RBC, and the effects on the spermatocytes and postmeiotic germ cells were assayed. Short-term cultures of human lymphocytes from a single donor were treated in vitro with 0.1 or 0.5 mM styrene oxide, and the effects on the chromosomes were determined. There was a significant increase in the total number of anomalies after treatment of the lymphocytes with 0.5 mM styrene oxide; this was due mainly to an increase in chromatid gaps. All tests on somatic and germ cells in vivo yielded negative results. Thus, styrene oxide appears to be capable of producing genetic damage in cells in vitro, but it could be less effective in vivo. (14 refs.)

78-4954 **The Induction of Tumours of the Digestive Tract and of Certain Other Organs in Rats Given T-2 Toxin, a Secondary Metabolite of *Fusarium sporotrichioides* (Meeting Abstract).** (Eng) Schoental, R. (Royal Veterinary Coll., London, England); Joffe, A. Z.; Yagen, B. *Br J Cancer* 38(1): 171; 1978. (1 ref)

78-4955 **Carcinogeneity of Betel Quid Ingredients Singly or in Combination Using Different Experimental Models (Meeting Abstract).** (Eng) Gothoskar, S. V. (Biology Div., Cancer Res. Inst., Tata Memorial Centre, Bombay 400012, India); Ranadive, S. N.; Shivapurkar, N. M.; Ranadive, K. J. *In: Summary Program and Abstracts of Papers. Proceedings of the 3rd Asian Cancer Conference Held by the Philippine Cancer Society under the Auspices of the Asian Federation of Organizations for Cancer Research and Control in Manila, 26-30 September, 1977.* Philippine Cancer Society. (Manila, Philippines): 184 pp.; 66-67; 1977. (no refs)

78-4956 **Fungal Contamination and Mycotoxin Detection of Powdered Herbal Drugs.** (Eng) Hitokoto, H. (Dept. Microbiology, Tokyo Metropolitan Res. Lab. Public Health, Shinjuku-ku, Tokyo, 160, Japan); Morozumi, S.; Wauke, T.; Sakai, S.; Kurata, H. *Appl Environ Microbiol* 36(2): 252-256; 1978.

A total of 49 powdered herbal drugs were analyzed for their mold profile and for the potential presence of aflatoxin, sterigmatocystin, and ochratoxin A. Mycotoxins were not detected in any samples. Of 69 strains of fungus isolated from the drugs, only one strain of *Aspergillus flavus* was capable of producing aflatoxin (type B_1, 0.15 μg/ml) on laboratory media. The drugs contained predominantly *Aspergillus* and *Penicillium* fungi. (14 refs.)

78-4957 **Differential Effect of Aflatoxin B_1 on Ribosomal RNA Synthesis of Rat Liver Depending on the Carcinogenic or Toxic Activity of the Compound (Meeting Abstract).** (Eng) Novi, A. M. (Pathologisches Institut, Universitat Dusseldorf, Moorenstrasse 5, D-4000 Dusseldorf, W. Germany); Wagner, G. *Hoppe Seylers Z Physiol Chem* 359(9): 1128; 1978. (2 refs)

78-4958 **Mycotoxins. Thin Layer Chromatographic Determination of Aflatoxin B_1 in Eggs: Collaborative Study.** (Eng) Nesheim, S. (Div. of Chemistry and Physics, Food and Drug Admin., Washington, DC, 20204); Trucksess, M. W. *J Assoc Off Anal Chem* 61(3): 569-573; 1978.

The effectiveness of two-dimensional thin-layer chromatography for determining aflatoxin B_1 (AFB_1) levels in hens eggs was tested collaboratively. Nine collaborators analyzed three known practice samples and nine unknown samples containing 0, 0.05, 0.10, or 0.30 nanogram (ng)/g AFB_2. Recoveries for the three positive levels were: 0-0.13 [av 98%, coefficient of variation (CV) 83%], 0.05-0.18 (av 102%, CV 36%), and 0.11-0.42 ng/g (av 93%, CV 31%), respectively. (6 refs)

78-4959 **Use of High Performance Liquid Chromatography Combined with Fluorescence Detection for the Identification and Estimation of Aflatoxins and Ochratoxin in Food.** (Eng) Hunt, D. C. (Dept. Industry, Lab. Government Chemist, Cornwall House, Stamford St., London SE1 9NQ, England); Bourdon, A. T.; Wild, P. J.; Crosby, N. T. *J Sci Food Agric* 29(3): 234-238; 1978.

A method was developed for the separation, identification, and estimation of aflatoxin B_1 (AFB_1), AFB_2, AFG_1, AFG_2, AFM_1, and ochratoxin A in foods at the μg/kg level. The food is extracted with aqueous acetonitrile, washed with

2,2,4-trimethylpentane, and any mycotoxins are reextracted into chloroform. The extract is purified by thin-layer chromatography. Any fluorescent bands are then removed and examined by high-pressure liquid chromatography. Recoveries at twice the detection limit varied from 40% to 95%. (8 refs)

78-4960 **Effect of Hypophysectomy and Aflatoxin B_1 on Rat Liver.** (Eng) Neal, G. E. (Toxicology Unit, MRC Labs., Woodmansterne Road, Carshalton, Surrey 5M5 4EF, England); Judah, D. J. *Cancer Res* 38(10): 3460-3467; 1978.

The effect of hypophysectomy (HPS) on aflatoxin B_1 (AFB)-induced liver carcinogenesis was studied in male Fischer rats. Four groups of rats were used: weanlings, small and large hypophysectomized (HPS-x) rats, and adult intact rats. Ingestion of 4 ppm AFB for 4-5 wk resulted in minimal changes in the livers of weanlings and HPS-x rats, but caused massive necrosis in the livers of the adult intact animals. This effect was not related to the amount of diet consumed. The liver necrosis in the adult intact animals may have been due to the presence of a large tetraploid hepatocyte population. The absence of these cells could account for the resistance of the weanlings. The considerable tetraploid hepatocyte population present in the large HPS-x rats was not susceptible to the necrogenic action of AFB, either fed to the rats or given as ip injections (2.0 mg/kg). Hepatic nucleic acid synthesis was reduced by HPS or the administration of AFB. In both cases, the effect was more marked in the tetraploid than in the diploid hepatocytes. Nucleic acid synthesis in the HPS-x rats was more resistant to inhibition by AFB than that in intact rats. This appeared to be due to the lower basal level of nucleic acid synthesis in the former, the final inhibited levels being similar in the two groups. The ability of the microsomal systems obtained from HPS-x rats to activate AFB did not appear to be significantly less than the ability of microsomes isolated from control rats. There may be a close correlation between the uptakes of AFB and steroid hormones into the liver, with the uptake mechanisms possibly being located in the tetraploid hepatocytes. HPS could protect against the effects of AFB by removing the steroid uptake mechanisms by which AFB enters the subcellular structures. (15 refs.)

78-4961 **Aflatoxin Contamination of Grains in Flooded Areas of Mathura, Uttar Pradesh (Letter to Editor).** (Eng) Mishra, R. S. (P.G. Dept. Botany, Bhagalpur Univ., Bhagalpur 812 007, Bihar, India); Singh, R. S. *Curr Sci (Bangalore)* 47(11): 396-397; 1978.

Thirty-six grain samples from fields that had been inundated by heavy rains were studied for mycotoxin contamination. *Aspergillus*, *Penicillium*, and *Rhizopus* were the main fungi associated with the samples. Aflatoxins were found in 18 samples. Aflatoxin B_1 was the most prevalent toxin (6-200 ppb); few samples contained aflatoxins B_2, G_1, and G_2, and the levels were < 10 ppb. (8 refs.)

78-4962 **Identification of the Principal Aflatoxin B_1-DNA Adduct Formed In Vivo in Rat Liver.** (Eng) Croy, R. G. (Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, MA, 02139); Essigmann, J. M.; Reinhold, V. N.; Wogan, G. N. *Proc Natl Acad Sci USA* 75(4): 1745-1749; 1978.

The products of in vivo covalent binding of activated aflatoxin B_1 (AFB_1) to DNA were investigated in male Fischer rats. The principal covalent product formed in liver DNA of rats treated with AFB_1 (2.0 mg/kg, ip) was identified as 2,3-dihydro-2-(N^7-guanyl)-3-hydroxyaflatoxin B_1. This compound was isolated in sufficient quantity for characterization by physicochemical techniques, including field-desorption mass spectrometry. This information, together with results of chemical methylation of the compound, proved that the major adduct formed between DNA and AFB_1 in vivo is identical to that produced in vitro when AFB_1 is incubated with DNA in the presence of a rat liver microsome activation system. Quantitative studies of the formation of this compound revealed a dose-dependent relationship between the level of its occurrence in liver DNA and AFB_1 doses over the range 0.125-1.0 mg/kg. (31 refs)

78-4963 **Effect of Vitamin A Deficiency and Excess on Aflatoxin Metabolism in the Rabbit.** (Eng) Bassir, O. (Dept. Biochemistry, Univ. Ibadan, Ibadan, Nigeria); Adekunle, A. A.; Okoye, Z. S. *Biochem Pharmacol* 27(5): 833-838; 1978.

The effect of a diet depleted of or supplemented with vitamin A on the in vitro metabolism of aflatoxin was investigated using liver fractions from three groups of weanling male rabbits. Group 1 was fed a vitamin A-deficient diet, and Groups 2 (controls) and 3 were fed a diet supplemented with 5,000 and 60,000 IU retinylpalmitate/kg diet, respectively. The animals were killed after the 28-day feeding period, and the liver fractions were isolated. During the feeding period, the liver vitamin A content of Group 1 decreased to 45% of that in Group 2, but the vitamin A content in the livers of Group 3 animals increased to 340% of that in Group 2. Only aflatoxin B_1 demethylase activity was significantly reduced in the marginally deficient rabbits. However, for both hydroxylation and demethylation of aflatoxin, the value for Group 3 tended to be less than that of Group 2, and aflatoxin B_1 hydroxylase activity tended to be higher in Group 1 than in Group 2. It appears that a gross vitamin A deficiency is not necessary to reduce aflatoxin B_1 demethylation in the rabbit. (29 refs)

78-4964 **The Estimation of Aflatoxin M_1 in Milk Using a Two-dimensional Thin-layer Chromatographic Method Suitable for Survey Work.** (Eng) Patterson, D. S. (Central Veterinary Lab., Weybridge, Surrey KT15 3NB, England); Glancy, E. M.; Roberts, B. A. *Food Cosmet Toxicol* 16(1): 49-50; 1978.

An existing method for the analysis of aflatoxin M_1 in cow's milk was modified by the introduction of two-dimensional thin-layer chromatography (TLC) and certain confirmatory tests. The smallest quantity of aflatoxin M_1 that is easily visible on two-dimensional TLC is 0.2 nanogram when it is applied in 5 μl chloroform. This corresponds to a quantitative analytical limit of 0.052 μg aflatoxin M_1/liter milk, but even smaller amounts can be detected if they are not quantitated, so that the detection limit is 0.03 μg/liter. This procedure is sufficiently sensitive to detect any aflatoxin M_1 carried over into milk from aflatoxin B_1 present in the cattle feed at the very low max level permitted by current regulations in the United Kingdom. (5 refs.)

78-4965 **Determination of Aflatoxins in Peanut Products Using Reverse Phase HPLC.** (Eng) Hurst, W. J. (Hershey Foods Res. Labs., P.O. Box 54, Hershey, PA, 17033); Toomey, P. B. *J Chromatogr Sci* 16(8): 372-376; 1978.

High-performance liquid chromatography was used to determine aflatoxin B_1, B_2, G_1, and G_2 in peanut products. This procedure can be applied to roasted and unroasted peanuts and to sweetened peanut matrixes with no interferences in the chromatography. It allowed the quantitative detection of all four aflatoxins at the 5- to 7-nanogram/kg level in <1.5 hr. (32 refs.)

78-4966 **Desmofibrinogenic Activity of Transamidases and Thiol Groups in Plasma and Tissues after Poisoning with Aflatoxin B_1.** (Pol) Zuch, A. (Zaklad Patologii Ogolnej i Doswiadczalnej AM, Instytut Fizjologii i Biochemii, ul. Mickiewicza 2c, 15-230 Bialystok, Poland); Januszko, T.; Poplawska, T. *Pol Arch Med Wewn* 59(2): 171-181; 1978.

Ip injection of aflatoxin B_1 (total dose: 0.56 mg/kg) into guinea pigs decreased the concentration and activity of plasma transamidases (FSF, coagulation factor XIII). A parallel transient decrease in desmofibrinogenic activity and in the concentration of lung and liver tissue transamidases was also observed. The increase in fibrinolytic activity and decrease in plasma levels of free thiol groups lasted longer (up to 10 days) than the changes in FSF. (18 refs)

78-4967 **Microsomal Activation of Aflatoxin B_1 and G_1 Metabolites Mutagenic in *Neurospora crassa* (Meeting Abstract).** (Eng) Ong, T. M. (Lab. Environmental Mutagenesis, NIEHS, Research Triangle Park, NC 27709). *Environ Health Perspect* 20: 234; 1977. (no refs)

78-4968 **Aflatoxin Observed by Fluorescent Microscopy in Primary Liver Cancer Patients from Zaire.** (Fre) Stora, C. (I.N.S.E.R.M., F.R.A. No. 12, Faculte de Medecine de Nice, Chemin de Vallombrose, 06034 Nice Cedex, France). *C R Acad Sci [D] (Paris)* 286(11): 917-920; 1978.

Biopsy samples from inhabitants of Zaire with hepatomas or cholangiocarcinomas of the liver were examined by fluorescence microscopy for the presence of aflatoxin B or G. The hepatoma tissue showed the blue fluorescence characteristic of aflatoxin B. Both the cytoplasm and nuclei of the tumor cells were highly fluorescent, with the most intense fluoresence being exhibited by the chromosomes. The cholangiocarcinoma cells were only slightly fluorescent; the fluorescence was observed in newly formed vessels and in the cytoplasm of the macrophages, which were abundant in zones of necrosis. Aflatoxin G was noted by an intense yellow-green fluorescence in the connective tissue surrounding the tumor nodes. No difference in fluorescence was observed between aflatoxins B1 and B2 or between G1 and G2 and their metabolites. (9 refs)

78-4969 **Hepatic Transformation of Aflatoxin and Its Carcinogenicity.** (Eng) Hsieh, D. P. (Dept. Environmental Toxicology, Coll. Agricultural and Environmental Sciences, Univ. California, Davis, CA, 95616); Wong, J. J.; Wong, Z. A.; Michas, C.; Ruebner, B. H. *In: Mechanisms of Carcinogenesis. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book B), 699 pp; 697-707; 1977.

The relationship between the carcinogenicity and mutagenicity of aflatoxins (AF's) is reviewed. The Ames mutagenicity assay was performed on several AF's and their metabolites. All the AF's tested required the presence of a rat liver postmitochondrial supernatant (S-9) for mutagenic activity, indicating that none of them is the active form and that all are precarcinogens. Aflatoxin B_1, (AFB_1) had the highest mutagenic activity, followed by AFL, AFG_1, AFM_1, and other derivatives. There was a good correlation between the in vitro bacterial mutagenicity of these compounds and their in vivo animal carcinogenicity. Hepatic S-9 systems for in vitro assays of AFB_1 bioactivation were obtained from duck, rat, monkey, mouse, and human livers. The in vitro bioactivation

ctivity of the liver from a particular species for AFB_1 cor-elated with the known sensitivity of that species to the car-inogenic effect of AFB_1. This was evident from the consist-nt ranking of the relative mutagenic activities of AFB_1 generated by the hepatic S-9 enzymes of the different species duck > rat > monkey > mouse > human) and the relative sus-eptibilities of the species to carcinogenic aflatoxicosis. The lata show that humans are less susceptible to carcinogenic aflatoxicosis than the relatively resistant monkey and mouse. 31 refs.)

78-4970 **Alpha Benzene Hexachloride Inhibition of Aflatoxin B_1-induced Hepatocellular Carcinoma. A Preliminary Report.** (Eng) Angsubhakorn, S. (Dept. Pathobiology, Faculty Science, Ramathibodi Hosp., Mahidol Univ., Bangkok 4, Thailand); Bhamarapravati, N.; Romruen, K.; Sahaphong, S.; Thamavit, W. *Experientia* 34(8): 1069-1070; 1978.

The effect of α-benzene hexachloride (BCH) on the induction of hepatocellular carcinoma by aflatoxin B_1 was studied in male albino Fisher rats. Rats were fed a diet containing 1 ppm AFB and/or 0.05% BHC for 10 or 20 wk. Rats were sacrificed at 10 or 65 wk. In animals sacrificed after 10 wk, the only histological change noted was hypertrophy of the hepatocytes in the centrilobular region in the BHC and BHC + AFB groups. The liver wt:body wt ratio in the BHC and BHC + AFB groups was significantly higher than that in the AFB and normal diet groups. In the long-term experiment, tumors were noted in all three AFB group rats that survived until 65 wk, as well as in two rats that died during weeks 56 and 59. Tumors were not detected in any of the BHC, BHC + AFB, or control rats that survived the experiment. Rats from these three groups that died during the experiment had no signs of preneoplastic change in the liver. The liver wt:body wt ratio of the AFB-fed rats was greater than that of rats fed BHC, BHC + AFB, or a control diet. These results suggest that BHC prevent the induction of liver tumors by AFB. (8 refs.)

78-4971 **Relationship Between Lipids and Scleroproteins in Asbestosis and Anthracosis.** (Rus) Belobragina, G. V. (Inst. Vocational Hygiene and Occupational Diseases, Sverdlovsk, USSR); El'nichnykh, L. N. *Gig Tr Prof Zabol* (3): 31-34; 1978.

In an attempt to evaluate the possible role of phospholipids in the pathogenesis of asbestosis and anthracosis, asbestos and anthracite dusts were administered intratracheally (50 mg) to albino rats. Rats were sacrificed within 7 days-17 mo of exposure, and the lung tissue was examined. Single administration of asbestos and anthracite dusts induced mild perinodular fibrosis and the gradual development of diffuse fibrosis. The total lipid level in the lung tissue of exposed rats was significantly greater than that in controls; the accumulation of total lipids and especially, phospholipids exceeded the accumulation of fibroproteins. These findings indicate that the relationships between total lipids and fibroproteins in asbestosis and anthracosis are similar to those in the development of presenile fibrosis. (21 refs)

78-4972 **Carcinogens and Analogs: Trace Analysis of Thirteen Compounds in Admixture in Wastewater and Human Urine.** (Eng) Nony, C. R. (Dept. Health, Education and Welfare, Food and Drug Admin., Natl. Center Toxicological Res., Jefferson, AR, 72079); Bowman, M. C. *Int J Environ Anal Chem* 5(3): 203-220; 1978.

Traces of 13 carcinogens and related compounds (aromatic amines and estrogens) in admixture in wastewater and human urine were determined by gas chromatography. Residues were detectable at the 0.1- and 1-ppb levels in the two liquids, respectively. Partition values for all pentafluoropropionyl derivatives in five solvent systems, structure verification by mass spectrometry, and adaptation of the method to work surfaces and air are provided. (18 refs)

78-4973 **Occupationally Related Incidence of Double Cancers: Four Cases of Transitional Cell Carcinoma of the Urinary Bladder with Other Cancers.** (Jpn) Matsushima, M. (Dept. Urology, Sch. Medicine, Toho Univ., Toho, Japan); Fukazawa, K.; Yagishita, T.; Hirose, K.; Miura, K.; Matsumoto, H.; Ando, K. *Acta Urol Jpn* 24(5): 409-416; 1978.

Four of 20 male dyestuff workers with transitional cell carcinoma (TCC) of the urinary bladder also had another occupationally related cancer. The 20 cases of TCC (including 1 of asynchronous bilateral ureteral tumors) were found among 90 workers who had been exposed to aromatic amines and who were subjected to periodic urine cytology tests. The four patients with metachronous double cancers were a 56-yr-old with TCC and an adenocarcinoma of the left lung, a 56-yr-old with TCC and a hepatoma, a 43-yr-old with TCC and a bile duct adenocarcinoma, and a 61-yr-old with TCC and a nonhormonal adrenocortical cancer. (28 refs.)

78-4974 **Enzymatic Changes in Peripheral Blood Leukocytes in Rats in Subacute Benzene Vapours Poisoning. Acid Phosphatase Activity in Lymphocytes.** (Eng) Moszczynski, P. (Internal Diseases Dept., ZOZ, 32-800 Brzesko, Poland); Starek, A. *Pol J Pharmacol Pharm* 30(1): 21-27; 1978.

Acid phosphatase (AcP) activity, its intracellular distribution in peripheral blood lymphocytes, and the activity of the lysosomal isoenzyme of acid phosphatase (AcP-L) were investigated in the serum of rats exposed to benzene vapor (27,000 mg/m^3, 6 hr daily, for 10 consecutive days). There was a statistically significant fall in total lymphocytes, AcP+ and AcP- lymphocytes, and granular lymphocytes and an increase in granular-diffuse and diffuse lymphocytes. Serum AcP-L was also increased. Benzene may increase the permeability of the lysosomal membranes. (24 refs)

78-4975 **Binding of Labeled Benzene Metabolites to Mouse Liver and Bone Marrow.** (Eng) Snyder, R. (Dept. Pharmacology, Thomas Jefferson Univ., Philadelphia, PA, 19107); Lee, E. W.; Kocsis, J. J. *Res Commun Chem Pathol Pharmacol* 29(1): 191-194; 1978.

The binding of benzene metabolites to liver and bone marrow was investigated in mice given twice daily doses of 440 or 880 mg/kg ^{3}H-benzene sc for 10 days, or 880 mg/kg/day sc for 10 days. Irreversible binding of the radioacticity to liver and bone marrow was related to the dose of ^{3}H-benzene administered SC over a 3 day period. Administration of 880 mg/kg twice daily definitely increased binding to liver and possibly to bone marrow over that observed with a single 880-mg/kg dose. Dividing the 880 mg dose into two daily doses of 440 mg/kg did not increase binding in either of these organs. Twice daily doses of 440 mg/kg resulted in increased binding throughout treatment in the liver, but in the bone marrow, the binding increased for days 1 to 6 and decreased between days 6 and 10. It is suggested that the increase in the liver was related to a marked reduction in the urinary metabolites of benzene between days 6 and 10, probably because of liver damage. By day 10, the marrow had lost its characteristic red color, indicating that the functional tissue had probably been replaced by fat. It is suggested that benzene binding to bone marrow is important in leukemogenesis. (5 refs)

78-4976 **Biological Behavior of N-[4-(5-Nitro -2-furyl)-2-thiazolyl] formamide Induced Carcinoma of the Transitional Epithelium in the Rat.** (Eng) Kiel, H. (Dept. Lab. Animals, Chemie Grunenthal GmbH, Zweifaller Strasse, D-5190 Stolberg, W. Germany); Adolphs, H. D.; Thiele, J.; Steffens, L. *Z Krebsforsch* 91(3): 267-277; 1978.

The incidence and selectivity of tumor induction by N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (FANFT) were determined in 45 female Wistar rats fed 0.188% FANFT for 8 mo, for an av weekly dose of 0.195 g/animal. At 12 mo, multiple papillomatous bladder tumors were found in all 30 rats available for assessment, but there were no distant metastases. Histologically, the tumors were papillary transitional cell carcinomas, and all bladder specimens showed infiltrative tumor growth. The tumors were Stages II-IV and Grades 2-3. In addition, there were considerable dysplastic changes in the urothelium with focal areas of intraepithelial carcinomas. There was no significant statistical relationship between tumor stage and grade or between grade and wt, but a correlation was established between tumor stages and wt ($p < 0.05$); ie, tumor wt increased with enhanced local tumor infiltration. After 12 mo, 36/60 kidneys were normal; 20/60 had dysplasia of the renal pelvis epithelium, in part with papillary folding; 2/60 had transitional cell carcinomas of the renal pelvis; and 4/60 had hydronephrosis. It is concluded that the FANFT-induced bladder tumor of the rat provides a suitable model for studying human bladder tumors. (31 refs)

78-4977 **The Initiation, Progress, and Diagnosis of Dog Bladder Cancer Induced by 4-Aminobiphenyl.** (Eng) Block, N. L. (Dept. Urology, Univ. Miami Sch. Medicine, PO Box 520875, Miami, FL); Sigel, M. M.; Lynne, A. B.; Ng, A. B.; Grosberg, R. A. *Invest Urol* 16(1): 50-54; 1978.

Beginning at age 4 mo, 24 female beagles were fed 4-aminobiphenyl 5 days/wk for 3.5 yr. Two dogs failed to develop detectable tumors, but 20 dogs developed tumors that progressed to transitional cell carcinomas Grades 2 and 3. Three basic patterns of response to the carcinogen were observed: (1) negative or minimal disease (4 dogs); (2) slow tumor progression with minor fluctuations in development (11 dogs); and (3) rapid tumor progression (9 dogs). The first positive diagnosis of neoplasia was made 15-34 mo after the beginning of treatment. Eleven dogs underwent surgery ranging from tumor sampling to cystectomy plus ureterosigmoidostomy. The tumors closely paralleled human bladder cancer in several characteristics, including histologic types and grades and patterns of metastasis. (16 refs.)

78-4978 **Metabolism of Bromobiphenyls.** (Eng) Kohli, J. (Guelph Waterloo Centre for Graduate Work in Chemistry, Dept. Chemistry, Univ. Guelph, Guelph, Ontario, Canada); Wyndham, C.; Smylie, M.; Safe, S. *Biochem Pharmacol* 27(8): 1245-1249; 1978.

The metabolism in vitro of 2-bromobiphenyls, 3-bromobiphenyl, and 4-bromobiphenyl was studied in male albino rabbits, and the mutagenicity of 4-bromobiphenyl in *Salmonella typhimurium* TA 1538 was investigated. The bromobiphenyl (PBB) substrates were given ip and the urine and feces collected for 7 days. A series of mono- and dihydroxylated metabolic products were isolated by preparative thin-layer chromatography. The nuclear magnetic resonance spectra of the two major 4-bromobiphenyl metabolites confirmed their structures as 4′-bromo-4-biphenolol and 4′-bromo-3,4-biphenyldiol. The metabolism of 4′(^{2}H)4-bromobiphenyl gave the corresponding monohydroxy compound that retained 61% of the deuterium; the catechol retained only 19%. The deuterium shift is consistent with metabolism via an arene oxide that rearranges to the phenol and undergoes hydra-

on/dehydrogenation to give the catechol. The retention of 9% of the deuterium in the catechol also indicates that some f the diol is formed via direct hydroxylation, as observed in ie metabolism of 4-chlorobiphenyl. Incubation of (^{3}H)4-romobiphenyl with rabbit liver microsomes gave two ajor degradation products, the chromatographic behavior f which was identical to that of the metabolites in vivo. -Bromobiphenyl was highly mutagenic to *S. typhimurium* A 1538 in the presence of a liver microsomal enzyme prepa-ation. The results indicate that metabolic degradation of BB is an important pathway for the detoxication of these hemicals via urinary excretion. (23 refs.)

8-4979 **Hepatocarcinogenicity of Polychlorinated Terphenyl (PCT) in ICR Mice and Its Enhance-ient by Hexachlorobenzene (HCB).** (Eng) Shirai, T. (First)ept. Pathology, Nagoya City Univ. Medical Sch., 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467, Japan); Miyata, Y.; Nakanishi, K.; Murasaki, G.; Ito, N. *Cancer Lett* (5): 271-275; 1978.

The carcinogenic effects of hexachlorobenzene (HCB) and olychlorinated terphenyl (PCT) were studied singly and in ombination when given po to ICR mice for 24 wk. The mice vere fed a basal diet supplemented with 10 or 50 ppm HCB, 50 or 500 ppm PCT, or 250 ppm PCT plus 50 ppm HCB. PCT alone induced liver tumors, nodular hyperplasias, and epatocellular carcinomas. HCB alone had no effect, but it nhanced the induction of liver tumors by PCT. It is known hat PCT accumulates in mouse liver, reaching a concentra-ion of 4-10 times that in the diet, and this may be a reason vhy the liver is the target organ for PCT carcinogenesis. The umors induced by PCT were histologically similar to those nduced by hepatocarcinogens such as α-benzene hexachlo-ide, polychlorinated biphenyl, and N-2-fluorenylacetamide. 10 refs)

8-4980 **Distribution and Excretion of Halogenated Xenobiotics (PCB, PBB, and Kepone) (Meeting Abstract).** (Eng) Matthews, H. B. (Pharmacokinetics Section, Lab. Pharmacology, NIEHS, Research Triangle Park, NC, 7709); Morales, N. M.; Kato, S.; McKinney, J. D.; Tuey, D. B. *Environ Health Perspect* 20: 233; 1977. (no refs)

78-4981 **Reaction Products of the Carcinogen N-Hydroxy-4-acetylamino-4′-fluorobiphenyl with DNA in Liver and Kidney of the Rat.** (Eng) Kriek, E. (Chemical Carcinogenesis Div., Antoni Van Leeuwenhoek-Huis, Netherlands Cancer Inst., Amsterdam, Netherlands); Hengeveld, G. M. *Chem Biol Interact* 21(2/3): 179-201; 1978.

The in vivo binding of 4-acetylamino-4′-fluorobiphenyl (AABP4′F) and 4-amino-4′-fluorobiphenyl (ABP4′F) residues to rat liver and kidney DNA was studied at various times after inoculation of male albino rats (inbred R-Amsterdam strain) with N-[G-^{3}H]hydroxy-AABP4′F (5 or 25 mg/kg). DNA preparations from both organs were hydrolyzed enzymatically at pH 8-9 with mixtures of DNase, snake venom phosphodiesterase and alkaline phosphatase from *Escherichia coli*. The enzymatic digests were analyzed by Sephadex LH-20 chromatography using synthetic N-([G-^{14}C]deoxyguanosin-8-yl)-ABP4′F as marker. Elution with 30% ethanol gave three major peaks of ^{3}H activity,one that consisted largely of N-(deoxyguanosin-8-yl)-ABP4′F decomposition products, a second that had chromatographic and chemical properties similar to those of 3-(deoxyguanosin-N^2-yl)-AAF and was persistent in both liver and kidneys, and a third that cochromatographed with the marker compound. Kinetic studies revealed that the third product was removed rapidly from liver and kidney DNA at equal rates (half time = 2 days). Approx 80% of the total radioactivity bound to DNA consisted of deacetylated material, which was removed at a much slower rate (half time = 10 days) in both organs. The initial rapid removal of all products in the kidney during the first 7 days (half time = 3.3 days) with the 25-mg/kg dose was probably due to toxic effects on the kidneys because this phenomenon was not observed with the 5-mg/kg dose. It was concluded that the overall removal of arylamine adduct in DNA proceeds much more slowly than the removal of N-(guanin-8-yl)arylamide moieties. Comparisons were made between these results and those obtained with acetylaminofluorene. (40 refs.)

78-4982 **Non-specific Tritiation of Some Carcinogenic Aromatic Amines.** (Eng) Breeman, G. E. (Chemical Carcinogenesis Div., Antoni van Leeuwenhoek-Huis, Netherlands Cancer Inst., Amsterdam, Netherlands); Kaspersen, F. M.; Westra, J. G. *J Labelled Compd Radiopharm* 14(5): 741-750; 1978.

2-Aminofluorene, 4-amino-3-methylbiphenyl, 4-aminobiphenyl, and 4-amino-4′-fluorobiphenyl were tritiated by acid-catalyzed exchange of the corresponding nitro compounds followed by catalytic reduction. The exchange reactions were carried out by heating the nitro compounds in ^{3}H-trifluoroacetic acid and adding a catalytic amount of trifluoromethanesulfonic acid. No loss of tritium could be detected during conversion of the tritiated nitro compounds into the corresponding amines by catalytic hydrogenation. Incorporation into the ortho position was $<4\%$. During the metabolic activation and binding of ^{3}H-N-acetyl-2-aminofluorene to rat liver DNA in vivo, no tritium exchange occurred. (7 refs.)

78-4983 **Effect of α-Benzene Hexachloride on 2-Fluorenylacetamide Carcinogenesis in Rats.** (Eng) Hiasa, Y. (First Dept. Pathology, Nara Medical Univ., 840 Shijo-cho Kashihara, Nara-ken 634, Nara, Japan); Ohshima, M.; Ohmori, T.; Murata, Y. *Gann* 69(3): 423-426; 1978.

The effect of α-benzene hexachloride (BHC) on the induction of hepatomas in male Wistar rats treated simultaneously with 2-fluorenylacetamide (2-FAA) was studied. Diets containing 0.025% 2-FAA (Group 1), 2-FAA + 0.06% BHC (Group 2), BHC (Group 3), or no additions (Group 4) were fed to the animals for 5 mo, followed by a stock diet for 4 wk. Hepatocellular carcinomas were observed only in 7/8 Group 1 rats; the livers of all these rats contained a few small cysts, and there were multiple hyperplastic nodules and moderate oval cell infiltration. Adenocarcinomas developed in 4/11 Group 2 rats, and the livers of all rats had multiple cysts with islands of parenchymal cells between them. There were a few hyperplastic nodules, and oval cell infiltration was slight. The adenocarcinomas, which were not found in any other groups, were small (max of 2 mm in diameter) and there were no metastases. The adenocarcinomas may originate from the bile ducts. Histopathological findings in Groups 3 and 4 were negative. (13 refs.)

78-4984 **Covalent Intercalative Binding to DNA in Relation to the Mutagenicity of Hydrocarbon Epoxides and N-Acetoxy-2-acetylaminofluorene.** (Eng) Drinkwater, N. R. (McArdle Lab. Cancer Res., Univ. Wisconsin Medical Center, Madison, WI, 53706); Miller, J. A.; Miller, E. C.; Yang, N. C. *Cancer Res* 38(10): 3247-3255; 1978.

The abilities of N-acetoxy-2-acetylaminofluorene (N-AAF) and a series of hydrocarbon epoxides to cause the unwinding of supercoiled simian virus 40 (SV40) DNA by covalent binding were measured by incubating the DNA with the compound at pH 7.4 and 37 C and then determining the superhelicity of the modified DNA by gel electrophoresis. The concentrations of the electrophiles required to fully unwind the supercoiled DNA ranged from 0.023 to > 3 mM in this ascending order: (±)-7β,8α-dihydroxy-9α,10α-epoxy-7,8,9,10-tetrahydrobenzo(a)pyrene, 1-pyrenyloxirane, 9-methyl-10-anthryloxirane, 6-chrysenyloxirane, 9-anthryloxirane, N-AAF, 9-phenanthryloxirane, 7-benzanthryloxirane, 2-naphthyloxirane, and styrene oxide (phenyloxirane). The frameshift mutagenicities of these compounds toward *Salmonella typhimurium* TA98 ranged from 540 to 0.001 revertants/nanomole, and they were well correlated with their abilities to cause DNA unwinding. The abilities of the compounds to induce missense mutations in *S. typhimurium* TA100 did not correlate as well with their activities in the DNA-unwinding assay. The hydrolysis rates of the compounds under the incubation conditions used for the DNA-unwinding assay were not correlated with their mutagenicities or their activities in causing DNA unwinding. Studies with ^{3}H-labeled N-AAF and (±)-[7-^{14}C]7β,8α-dihydroxy-9α,10α-epoxy-7,8,9,10-tetrahydrobenzo(a)pyrene indicated that complete unwinding of the supercoiled DNA required binding of about 0.05 hydrocarbon residue/nucleotide. The changes in superhelicity of the SV40 DNA upon treatment with these two electrophiles were confirmed by electron microscopy; no denaturing of the modified DNA was observed. These data suggest a model of covalent intercalative binding for the interaction of these compounds with DNA. (49 refs.)

78-4985 **Microsomal Metabolism of Arylamides by the Rat and Guinea Pig--I. Oxidation of N-3-Fluorenylacetamide at Carbon-Atom-9--A Major Metabolic Reaction.** (Eng) Kaplan, E. (Lab. Cancer Res., Veterans Admin. Hosp., Minneapolis, MN, 55417); Gutmann, H. R.; Emory, T. H. *Biochem Pharmacol* 27(11): 1581-1589; 1978.

The N-hydroxylation of N-3-fluorenylacetamide (3-FAA) by hepatic microsomes of untreated and 3-methylcholanthrene (3-MC; 20 mg/kg ip)-treated male Duncan-Hartley guinea pigs and male Sprague-Dawley rats was investigated. The N-hydroxylation by microsomes of both species was of the same low order. Both guinea pig and rat hepatic microsomes converted 3-FAA to N-(9-hydroxy)-3-FAA and to N-(9-oxo)-3-FAA. The former was the major product of 3-FAA hydroxylation by hepatic microsomes of both species, and it even exceeded the formation of N-(7-hydroxy)-3-FAA, the principal phenolic metabolite of 3-FAA. The amounts of N-(9-oxo)-3-FAA formed were about one-third those of N-(9-hydroxy)-3-FAA. In contrast to the formation of phenolic metabolites, the hydroxylation of 3-FAA to N-(9-hydroxy)-3-FAA was not increased by pretreatment of guinea pigs or rats with 3-MC. Similarly, pretreatment of rats with phenobarbital (80 mg/kg ip) did not enhance the yield of N-(9-hydroxy)-3-FAA. CO inhibited the formation of N-(9-hydroxy)-3-FAA by 80%. It is concluded that the formation of N-(9-hydroxy)-3-FAA is catalyzed by a microsomal hemoprotein not identical with cytochrome P_1-450 or P-450. In contrast, experiments in rats revealed that N-2-fluorenylacetamide (2-FAA) was a poor substrate for hydroxylation to N-(9-hydroxy)-2-FAA. The susceptibility of 3-FAA to hydroxylation at carbon atom 9 of the fluorene moiety may be rationalized by resonance structures in which carbon atom 9 is positively charged and acts as an electrophilic center. Similar resonance structures cannot be written for 2-FAA. (29 refs.)

78-4986 **Antibodies to DNA Modified by the Carcinogen N-Acetoxy-N-2-acetylaminofluorene.** (Eng) Leng, M. (Centre de Biophysique Moleculaire, 1A, avenue de la Recherche Scientifique, 45045 Orleans Cedex, France); Sage, E.; Fuchs, R. P.; Daune, M. P. *FEBS Lett* 92(2): 207-210; 1978.

The immunogenicity of native DNA modified by reaction with N-acetoxy-N-2-acetylaminofluorene (AAAF) was investigated. In rabbits, this DNA induced the synthesis of antibodies that specifically recognized AAF-substituted DNA. A method for purifying the antibodies is described, and association constants for the binding of the antibodies and several ligands are reported. (17 refs.)

8-4987 **Mutagenesis of Chinese Hamster Cells In Vitro by Combination Treatments with Methyl Methanesulfonate and N-Acetoxy-2-acetylaminofluorene.** (Eng) Myhr, B. C. (Somatic Cell Genetics Section, Biology Branch, NCI, Bethesda, MD, 20014); DiPaolo, J. A. *Cancer Res* 8(8): 2539-2543; 1978.

The lethal and mutagenic consequences of exposing Chinese hamster V79 cells to modify toxic doses of methyl methanesulfonate (MMS) followed at different time intervals by a strongly mutagenic dose of N-acetoxy-2-acetylaminofluorene (AcAAF) are described. Treatment with 500 μM MMS resulted in 5% survival of cloning ability and approx four azaguanine-resistant mutants per 10^5 survivors. Treatment with 7 μM AcAAF produced 10 times as many mutants, and survival was 7%. However, when V79 cells were treated with μM AcAAF after MMS (250-1,000 μM), a lethal synergism occurred that increased the lethality of the MMS pretreatment; the resulting lethality was unaffected by increasing the time interval between treatments from 1 to 48 hr. Lethal synergism was also observed at a constant dose of MMS (500 μM) and increasing doses of AcAAF (0.5-2.5 μg/ml). In contrast, no significant change in mutant frequency from that induced by AcAAF alone was found for treatment intervals of 1-63 hr. This result contrasts with a previously observed sixfold enhancement of AcAAF-induced transformation of Syrian hamster embryo cells similarly exposed, with a 48-hr interval between treatments. The difference in the response of these two cell types illustrates the difficulties in attempting to extrapolate the known correlation between individual mutagen and carcinogen treatments to combination treatments when different cell types are used for the two cellular responses. Thus, conclusions about a mutagenic mechanism for in vitro transformation must be derived from mutagenesis and transformation studies of the same cell type. (14 refs)

78-4988 **Culture of Hamster Hepatocytes Capable of High Rates of Carcinogen Metabolism (Meeting Abstract).** (Eng) Poiley, J. A. (Chemical Carcinogenesis Section, Frederick Cancer Res. Center, Frederick, MD, 21501); Raineri, R.; Cavanaugh, D.; Schuman, R.; Pienta, R. J. *In Vitro* 14(4): 336-337; 1978. (no refs)

78-4989 **Interaction of Aliphatic N-Hydroxylamines with Microsomal Cytochrome P450: Nature of the Different Derived Complexes and Inhibitory Effects on Monoxygenases Activitives.** (Eng) Mansuy, D. (Laboratoire de Chimie, l'Ecole Normale Superieure, 24 rue Lhomond, 75231 Paris Cedex 05, France); Rouer, E.; Bacot, C.; Gans, P.; Chottard, J. C.; Leroux, J. P. *Biochem Pharmacol* 27(8): 1229-1237; 1978.

The interactions of aliphatic primary N-hydroxylamines with rat liver microsomal cytochrome P450 was studied under conditions of oxidative metabolism. The microsomes were obtained from male Sprague-Dawley rats treated with sodium phenobarbital (SPB; 80 mg/kg/day ip for 3 days) or 3-methylcholanthrene (MCA; 20 mg/kg/day ip for 2 days). Primary N-hydroxylamines, RR'R''CNHOH, produced difference spectra of liver microsomes with peaks around 420 nanometers (nm) and troughs around 392 nm, possibly as the result of the hydroxylamines binding to cytochromes P450-Fe(III) through their oxygen atoms. The hydroxylamines interacted with dithionite- or NADPH-anaerobically reduced microsomes, giving peaks around 423 nm. In the presence of NADPH, oxygen, and microsome, all type RR'CNHOH hydroxylamines formed a 455 nm spectrum corresponding to cytochrome P450-Fe(II)-RR'CHNO complexes. These hydroxylamines strongly inhibited aniline hydroxylase, p-nitroanisole -O- demethylase, and 7-ethoxycoumarin -O- deoxylase activities of SPB-pretreated rat liver microsomes. These inhibitory effects were related to the ability of the hydroxylamines to form 455-nm absorbing complexes whose nitrosoalkane ligands were not displaced by oxygen. The general formation of nitrosoalkane-cytochrome P450 complexes and their inhibitory effects on monooxygenases should be taken into account in pharmacology, especially in the case of drug associations including an amino compound susceptible to metabolic oxidation to a primary or secondary nitrosoderivative. (47 refs)

78-4990 **Xenobiotic Metabolism in Marine Species Exposed to Hydrocarbons (Meeting Abstract).** (Eng) James, M. O. (Marine Pharmacology and Biomedicine Section, Lab. Pharmacology, NIEHS Lab. at C.V. Whitney Marine Lab., St. Augustine, FL, 32084); Bowen, E. R.; Weatherby, R. P.; Bend, J. R. *Environ Health Perspect* 20: 228; 1977. (no refs)

78-4991 **Histofluorescence of 3-Methylcholanthrene Metabolites in the Rat Pancreas.** (Eng) Black, O. (Gastroenterology Res. Labs., Forest Hills Div., Veterans Admin. Hosp., Augusta, GA, 30904). *Gastroenterology* 75(3): 438-444; 1978.

The pancreases of male Long-Evans rats were treated in vivo and in vitro with 3-methylcholanthrene (MC) and examined by histofluorescence techniques to determine the cell of origin of induced pancreatic tumors. For the in vitro studies, frozen sections were mounted on glass slides and dipped for 2 sec into a soln of 2 mg/ml MC dissolved in acetone:ether. The slides were then incubated for 60 min in a soln containing NADH, $MgCl_2$, and KCl. These sections revealed that acinar and ductal epithelium had equal fluorescence, which suggested equal metabolic capability. For the in vivo experiments, 10 mg MC was injected ip and the animals were killed 60 min later. Two additional rats were provided with biliary cannulas to divert bile from the pancreatobiliary ducts. Frozen sections were prepared and examined. Fluorescence was con-

centrated in the epithelium and lumen of the ducts. Animals with diversion of bile from the pancreatobiliary ducts had a similar intensity and distribution of fluorescence. These studies indicated that ductal epithelium was exposed to greater concentrations of carcinogen than nonductal epithelium, and they offer a possible explanation as to why ductal epithelium is more likely to undergo neoplastic transformation. (24 refs.)

78-4992 **Experimental Production of Brain Tumours in the Albino Mice (Meeting Abstract).** (Eng) Sarasa Bharati, R. (Madras Medical Coll., Madras, India); Arumugam, S. *J Neuropathol Exp Neurol* 37(5): 590; 1978. (no refs)

78-4993 **Separation and Identification of 3-Methylcholanthrene-related Compounds by Gas Chromatography-Mass Spectrometry.** (Eng) Takahashi, G. (Dept. Pathology, Chest Disease Res. Inst., Kyoto Univ., 53 Shogoin Kawahara-cho, Sakyo-ku, Kyoto 606, Japan). *Gann* 69(3): 437-439; 1978.

Eleven synthesized derivatives of 3-methylcholanthrene (3-MC) were rapidly separated, identified, and quantified by gas chromatography-mass spectrometry (GS-MS). Hydroxyl derivatives were silylated, and all chemicals were applied to columns of OV-1 and Dexsil-300 at a constant temperature of 260 and 290 C, respectively. A strong relative intensity of the mass spectra of all derivatives was obtained at an ionization voltage of 20 electron volts, and most of the molecular ions gave base peaks. Although separation was incomplete by GC, mass fragmentography plotted against molecular ions satisfactorily separated all the standard derivatives examined. (5 refs)

78-4994 **Measurement of H-2 Antigen and Immunogenicity of Methylcholanthrene-induced Murine Sarcomas.** (Eng) Pearson, T. (MRC Lab. Molecular Biology, Hills Road, Cambridge CB2 2QH, England); Sikora, K.; Lennox, E. *Br J Cancer* 37(4): 530-535; 1978.

The possible relationship between amounts of tumor-specific transplantation antigen (TSTA) and H-2 antigen was investigated using tumors induced in B10 or B10.BR mice by sc injection of 0.5 mg 3-methylcholanthrene. The strength of the TSTA was measured by a transplantation assay, the amount of H-2 antigen by absorption of a specific antiserum. Cell suspensions of tumors taken directly from the animal were shown to be contaminated by host cells that made a substantial contribution to the H-2 assay. Since this contamination was lost after several in vitro passages, the amount of H-2b on the tumor cells was assayed after three in vitro passages. A plot of the antigenic ratios vs the relative amount of H-2b indicated that the tumors varied greatly in both their degree of immunogenicity and their expression of H-2b. For most of the tumors, there was no obvious correlation between the two. However, the two most strongly immunogenic tumors expressed relatively little measurable H-2, and the most weakly immunogenic tumor expressed a fair amount. (13 refs)

78-4995 **Metabolic Activation of 3-Methylcholanthrene and Its Metabolites to Products Mutagenic to Bacterial and Mammalian Cells.** (Eng) Wood, A. W. (Dept. Biochemistry and Drug Metabolism, Hoffman-La Roche Inc., Nutley, NJ, 07110); Chang, R. L.; Levin, W.; Thomas, P. E.; Ryan, D.; Stoming, T. A.; Conney, A. H.; Thakker, D. R.; Jerina, D. M. *Cancer Res* 38(10): 3398-3404; 1978.

3-Methylcholanthrene (3-MC) and six of its metabolites were tested for their ability to be metabolized by either hepatic microsomes from Aroclor 1254-pretreated rats or a purified hepatic cytochrome P-450-dependent monoxygenase system to products mutagenic to bacterial and mammalian cells. With *Salmonella typhimurium* strain TA98 as a target for mutagens and microsomes as the source of metabolizing enzyme, 1-hydroxy-3-MC was metabolically activated to a 10-fold greater extent than 3-MC and was the most active compound tested. 1,9,10-Trihydroxy-9,10-dihydro-3-MC (TD-3-MC) and 3MC-2-one, the second and third most active compounds, respectively, were also activated to a greater extent than 3-MC; 2-hydroxy-3-MC was equipotent to the parent hydrocarbon. 3-MC-1-one was less active than 3-MC and 11,12-dihydroxy-11,12-dihydro-3MC was inactive. With the highly purified and reconstituted monoxygenase system as the enzyme source, TD-3-MC was activated to a 20-fold greater extent than 3-MC and was the most active compound. 3-MC-2-one and 1-hydroxy-3MC were the second and third most active compounds. 3-MC, 3-MC-1-one, and 2-hydroxy-3-MC were poorly activated. When *S. typhimurium* TA100 was used to detect mutations, TD-3-MC was metabolically activated to the greatest extent by both hepatic microsomes and the purified monooxygenase system. The metabolites of this compound were 15 and 100 times more mutagenic than those formed from 3-MC when the microsomes and the purified monooxygenase system, respectively, were the enzyme source. 3-MC-2-one was the second most active substrate with either enzyme source. Although 3-MC-1-one was the third most active substrate in the presence of microsomes, it was the least active with the purified enzyme system. 1-Hydroxy-3-MC, the third most active substrate with the enzyme system, was the least active when activated by microsomes. When hepatic microsomes from Aroclor 1254-pretreated rats were the source of the monooxygenase activity, the compounds had the same relative mutagenic activities in Chinese hamster V79 cells as they did in *S. typhimurium* TA100. Thus, the mutagenic activity of 3-MC metabolites is dependent on both the metabolic activating system and the target cell used to detect mutations. (2 refs.)

78-4996 **Identification of the Proximate Form of the Carcinogen 15,16-Dihydro-11-methylcyclopenta-[a]phenanthren-17-one (Meeting Abstract).** (Eng) Coombs, M. M. (Chemistry Dept., Imperial Cancer Res. Fund, London, England); Bhatt, T. S.; Kissonerghis, A. M. *Br J Cancer* 38(1): 192; 1978. (1 ref)

78-4997 **Quantitative Mutation Studies with a Series of Polycyclic Hydrocarbon Derivatives (Meeting Abstract).** (Eng) Newbold, R. F. (Chemical Carcinogenesis Div., Pollards Wood Res. Station, Nightingales Lane, Chalfont St. Giles Bucks, England); Amos, J.; Brookes, P. *Br J Cancer* 38(1): 170; 1978. (no refs)

78-4998 **Comparative Studies on the Covalent Binding of the Carcinogen Benzo(a)pyrene (BP) to DNA in Various Model Systems (Meeting Abstract).** (Eng) Jaggi, W. (Inst. Toxicology, ETH/Univ. Zurich, CH-8603 Schwerzenbach, Switzerland); Lutz, W. K.; Schlatter, C. *Experientia* 34(7): 925; 1978. (no refs)

78-4999 **Viral Antigen Induction and Mutability of Different Genetic Loci by Metabolically Activated Carcinogenic Polycyclic Hydrocarbons in Cultured Mammalian Cells.** (Eng) Huberman, E. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830). *In: Human Risk Assessment. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book C), 583 pp.; 1521-1535; 1977.

A possible relationshipbetween the degree of carcinogenicity of a series of polycyclic hydrocarbons and their ability to exhibit gene derepression representing an epigenetic process and/or to induce somatic mutations at different genetic loci was investigated. The induction of polyoma virus capsid antigen (PVCA) (which was detected by immunofluorescence) in an inducible PV-transformed rat embryo cell line was used to test for gene derepression. Somatic mutations were determined in Chinese hamster cells by genetic markers that affect the surface membrane, nucleic acid synthesis, and protein synthesis. The percentage of cells that synthesized PVCA was not significantly increased by treatment with noncarcinogenic hydrocarbons. Dibenz(a,h)anthracene, a weak carcinogen in vitro increased the proportion of cells that synthesized PVCA eightfold. The more potent carcinogens, 3-methylcholanthrene (3-MC), benzo(a)pyrene (BP), and 7,12-dimethylbenz(a)anthracene, increased the proportion of cells producing PVCA by 120-, 150-, and 180-fold, respectively. These results demonstrate a relationship between the carcinogenicity of polycyclic hydrocarbons and their ability to induce PVCA synthesis. There was also a correlation between mutagenicity and carcinogenicity. The noncarcinogens did not induce mutation, but 3-MC and BP enhanced the mutation frequency 60-280 times for the three genetic markers tested. The major mutagenic metabolite of BP was identified as (±)-7α,8β-dihydroxy -9β,10β- epoxy-7,8,9,10-tetrahydrobenzo(a)pyrene. The results suggest that both somatic mutations and epigenetic processes such as gene derepression may be involved in tumor formation by chemical carcinogens. (41 refs)

78-5000 **Morphological Transformation of C3H/10T1/2 Cells Subcultured at Low Cell Densities.** (Eng) Haber, D. A. (Genetic Toxicology Group., Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, MA, 02139); Thilly, W. G. *Life Sci* 22(18): 1663-1674; 1978.

Morphological transformation of C3H/10T1/2 cells treated with various concentrations of benzo(a)pyrene (BP) was measured following subculture of the cells at low cell densities. Subconfluent cultures exposed to 0.2-40 μM BP were allowed to grow to confluence, trypsinized, and reseeded at cell densities ranging from 5 to 2,300 surviving cells/cm². These secondary cultures were examined for morphological transformation after 8 to 9 wk incubation. Treated cells grown in virtual isolation (approx 5 surviving cells/cm²) exhibited a transformation frequency of 0.2%-14.5%. At these initial cell densities, transformation frequency was not significantly dependent on BP concentration. However, BP-treated cells reseeded at 11-2,300 surviving cells/cm² showed both density-dependent transformation frequencies and BP concentration dependence of transformation. The subculturing of treated cells did not affect the BP concentration dependence of focus formation. Cell density-dependent suppression of morphological transformation appears to be associated with colony interactions. BP at low concentrations appears to induce transformation potential via a nonmutational mechanism; at the higher concentrations used in this study, BP appears to result in a decline in contact-mediated inhibition phenomena. (16 refs.)

78-5001 **Toxic and Transforming Effects of Polycyclic Hydrocarbons in Fetal Hamster Lung-Cell Cultures. I. Benzo(a)pyrene.** (Eng) Emura, M. (Abteilung fur Experimentelle Pathologie, Medizinische Hochschule Hannover, Karl-Wiechert-Allee 9, 3000 Hannover 61, W. Germany); Richter-Reichhelm, H. B.; Mohr, U. *Cancer Lett* 4(6): 343-348; 1978.

The feasibility of using fetal Syrian golden hamster lung cell cultures of mixed population at early passages for the quantification of the toxic and carcinogenic effects of benzo(a)pyrene (BP) was determined. BP was dissolved in dimethyl sulfoxide (DMSO) and the stock soln diluted to final concentrations of 1.0, 0.75, 0.5, 0.25, 0.1, or 0.05 μg/ml. The

plating efficiency of the fetal lung cells at two to four passages varied between 1% and 4%, but this value could be held fairly constant at approx 4% by the addition of 0.025-0.2 IU/ml insulin. The colony-forming ability of the cells could be reduced by increasing the insulin concentration at constant BP concentrations. Thus, the toxic effects of BP were enhanced by the presence of insulin. The results of previous studies suggest that insulin may stimulate the cellular intake of BP or activate membrane-bound BP-metabolizing enzymes. Morphologically, only fibroblastic cell colonies were transformed. In additional studies, the insulin concentration was then held at 0.2 IU/ml and the cells were treated with various doses of BP and DMSO. At BP concentrations of 0.05 and 0.25 μg/ml, transformation rates were about 1%; however, total colony survival decreased with increasing BP concentrations. BP appeared to be more toxic to endothelial or epitheliallike cells than fibroblastic ones, but DMSO showed the opposite effect. DMSO was more toxic in the presence of 0.2 IU insulin/ml medium than without insulin or at insulin concentrations of 0.025 or 0.1 IU/ml. (9 refs.)

78-5002 **A Model System for Evaluating the Role of Dietary Fiber in Chemical Carcinogenesis.** (Eng) Clinton, S. K. (Sch. Basic Medical Sciences, Univ. Illinois, Urbana, IL, 61801); Truex, C. R.; Visek, W. J. *Biochem Pharmacol* 27(9): 1393-1396; 1978.

A model system for investigating the role of dietary fiber in intestinal cancer is presented. Female Sprague-Dawley rats were maintained on diets with or without benzo(a)pyrene (BP) and with or without wheat bran. Wheat bran prevented the induction of aryl hydrocarbon hydroxylase by BP in the exposed intestinal epithelium. This model can be used to examine the effects of this and other fibers on other segments of the intestinal tract. (14 refs.)

78-5003 **Photodynamic Effect of 3,4-Benzpyrene on Thermo-sensitive Mutants of *Escherichia coli* B.** (Eng) Molina, A. M. (Istituto di Microbiologia dell'Universita, Via Laterina, 8, 53100 Siena, Italy); Calegari, L.; Calendi, E. *Boll Ist Sieroter Milan* 57(2): 134-139; 1978.

The sensitivity of temperature-sensitive (ts) mutants of *Escherichia coli* B to the lethal photodynamic effect of benzo(a)pyrene (BP) was studied. These mutants were chosen for their inability to form colonies at 40 C. For comparison, two mutants that retained the ability to grow at 40 C were also tested. Cultures of the mutants were incubated with 10^{-5} M BP for 45 min at 30 C and then irradiated, in a glass water-bath at 20 C, with a 500-W quartz lamp 40 cm away. Mutants were removed at various times over a period of 25 min. The ts mutants had a significantly increased sensitivity to the photodynamic effect of BP; this effect was not observed in the two mutants able to grow at 40 C. It appeared unlikely that an alteration of the DNA was responsible for the increased sensitivity. The results indicate that irradiated BP can exert its action on proteins in vivo and that the presence of a protein with an impaired structure may be responsible not only for temperature sensitivity but also for increased susceptibility to the irradiated BP. However, temperature sensitivity and sensitivity to the photodynamic effect were not always correlated. This may be due to the type of amino acid substitution in the altered protein or to the position of the altered protein in the cell. (20 refs.)

78-5004 **Carcinogenic Activation of Benzo(a)pyrene by Iodine and Ferric Chloride in the Respiratory Tract of Syrian Golden Hamsters.** (Eng) Stenback, F. (Dept. Pathology, Univ. Oulu, Kajaanintie 52 D, SF-Oulu 22, Finland); Rowland, J. *Experientia* 34(8): 1065-1066; 1978.

The effect of iodine (I_2) and ferric chloride ($FeCl_3$) dusts on benzo(a)pyrene (BP)-induced respiratory tract carcinogenesis was studied in six groups of 48 Syrian golden hamsters. All chemicals were administered by intratracheal instillation weekly for 20 wk. Group 1 received 0.5 mg BP; Group 2 received 0.20 mg I_2; Group 3 received BP + I_2; Group 4 received 0.16 mg $FeCl_3$; Group 5 received BP + $FeCl_3$; and Group 6 received 0.20 ml saline. Three of seven tumor-bearing animals (TBA) in Group 1 had respiratory tract tumors (RTT): a laryngeal papilloma, a tracheal papilloma, and an accumulation of squamous cells arranged in a glandular fashion and a tracheal papilloma. There were no RTT in the five Group 2 TBA. Seventeen RTT were noted in 19 Group 3 TBA: there were 2 laryngeal papillomas, 19 tracheal papillomas, 2 tracheal squamous cell carcinomas, 6 adenosquamous lesions, 9 peripheral adenomatoid lesions, and 2 each of bronchial and lung papillomas, squamous cell carcinomas, and adenomas. No RTT were noted in two Group 4 TBA. Six RTT were noted in 12 Group 5 TBA: there were 6 tracheal papillomas and 6 peripheral adenomatoid lesions. No RTT tumors were noted in the one Group 6 TBA. The specific chemical binding of hydrocarbons with biological molecules requires that the compounds be activated by cellular hydroxylating enzymes. Several hydroxylases require transitional metals for enzymic activity, and this suggests that metals may be of prime importance in hydroxylation. Covalent binding of BP and similar compounds to nucleic acids is also produced by I_2. (11 refs.)

78-5005 **Increase of Urinary Putrescine in 3,4-Benzopyrene Carcinogenesis and Its Inhibition by Putrescine.** (Eng) Fujita, K. (Inst. Comprehensive Medical Science, Fujita-Gakuen Univ. Sch. Medicine, Toyoake, Aichi 470-11, Japan); Nagatsu, T.; Shinpo, K.; Maruta, K.; Takahashi, H.; Sekiya, A. *Cancer Res* 38(10): 3509-3511; 1978.

The effect of putrescine on benzo(a)pyrene (BP)-induced carcinogenesis was determined in female BALB/c mice. A sig-

nificant increase in putrescine was noted in the urine of mice with tumors induced by a single sc injection of 2.52 mg BP in 0.5 ml tricaprylin soln. However, when 10 mg putrescine was added to the BP soln, the development of tumors was completely inhibited and the increase in urinary putrescine was simultaneously suppressed. Animal wt data for a control group receiving only putrescine indicated that the inhibitory effect of putrescine was not due to its toxicity. (7 refs.)

78-5006 **Role of Talc and Benzo(a)pyrene in Respiratory Tumor Formation. An Experimental Study.** (Eng) Stenback, F. (Dept. Pathology, Univ. Oulu, 90220 Oulu 22, Finland); Rowland, J. *Scand J Respir Dis* 59(3): 130-140; 1978.

Morphologic alterations induced by 18 weekly intratracheal instillations of talc (3 mg/0.2 ml saline) or talc + benzo(a)pyrene (BP: 3 mg of each/0.2 ml saline) were studied in Syrian golden hamsters. Only three benign lung lesions were found in 48 hamsters treated with talc alone, and there were no detectable dust deposits, granulomas, or mesothelial proliferations. In contrast, 123 respiratory tumors were found in the 48 hamsters treated with talc + BP, 84 of which were malignant. Tumors were found in the larynx [6 papillomas, 3 squamous cell carcinomas (SCC)], trachea and main bronchi (6 papillomas, 8 SCC, 1 adenocarcinoma, 4 undifferentiated carcinomas), and peripheral bronchi and lungs (27 adenocarcinomas, 19 SCC, 8 undifferentiated carcinomas, 1 hemangioma, 1 adenoma). It appears that, in the hamster, talc has no carcinogenic activity itself but it does influence the activity of BP. (32 refs.)

78-5007 **Excisability and Persistence of Benzo(a)pyrene DNA Adducts in Epithelioid Human Lung Cells.** (Eng) Feldman, G. (Dept. Biochemistry and Molecular Biology, Univ. Florida, J. H. Miller Health Center, Gainesville, FL, 32610); Remsen, J.; Shinohara, K.; Cerutti, P. *Nature* 274(5673): 796-798; 1978.

The excisability and persistence of the covalent DNA adducts produced in the epithelioid human alveolar tumor cell A549 by benzo(a)pyrene (BP) were studied by high-pressure liquid chromatography. Chromatograms of total DNA and of micrococcal nuclease-resistant core DNA were made of digests from A549 cells that had been exposed to ^{14}C-thymidine and ^{3}H-BP (1.3 μM) and incubated for 0 to 72 hr. Peak I contained exclusively (7R)N^2-(10-[7β,8α,9α-trihydroxy-7,8,9,10-tetrahydrobenz(a)pyrene]yl)deoxyguanosine (BP diol-epoxide I-dG), and peak II contained approx 80% (7R or 7S) N^2-(10-[7β,8α,9β-trihydroxy- 7,8,9,10-tetrahydrobenzo(a)pyrene]yl)deoxyguanosine (BP-diol epoxide II-dG). Ratios of ^{3}H/^{14}C were used to relate the lesion concentration to the amount of DNA present during BP treatment. They were comparable at 0 hr posttreatment incubation for total DNA (peak I, 0.302; peak II, 0.090) and for nucleosomal core DNA (0.296; 0.070), and they remained comparable throughout the incubation period, decreasing with time. Excision essentially stopped by 72 hr, leaving a persistent fraction of lesions of 0.55 for BP diol-epoxide I-dG and of 0.40 for BP diol-epoxide II-dG. Thus, A549 cells possessed only a limited capacity to remove covalent DNA-BP adducts from their DNA. The poor repairability by excision of these and related lesions in human lung cells may represent a factor in lung carcinogenesis by polycyclic aromatic hydrocarbons. (13 refs.)

78-5008 **Modulation of the In Vivo Binding of the Carcinogen Benzo(a)pyrene (BP) to Rat Liver DNA by Selective Induction of Microsomal or Nuclear Aryl Hydrocarbon Hydroxylase Activity (AHH) (Meeting Abstract).** (Eng) Viviani, A. (Inst. Toxicology, ETH/Univ. Zurich, CH-8603 Schwerzenbach, Switzerland); Lutz, W. K. *Experientia* 34(7): 931; 1978. (no refs)

78-5009 **Repair of DNA Damage Induced by Benzo(a)pyrene Diol-Epoxides I and II in Human Alveolar Tumor Cells.** (Eng) Cerutti, P. A. (Dept. Biochemistry and Molecular Biology, J. Hillis Miller Health Center, Univ. Florida, Box J-245, Gainesville, FL, 32610); Sessions, F.; Hariharan, P. V.; Lusby, A. *Cancer Res* 38(7): 2118-2124; 1978.

Repair of DNA damage induced by the proximate benzo(a)pyrene (BP) metabolites, (±)-7β,8α-dihydroxy-9α,10α-epoxy- 7,8,9,10-tetrahydrobenzo(a)pyrene (diol-epoxide I) and (±)-7β,8α-dihydroxy -9β,10β- epoxy-7,8,9,10-tetrahydrobenzo(a)pyrene (diol-epoxide 2) was studied in the human alveolar tumor line A549. The fragmentation and subsequent reconstitution of DNA parent strands upon treatment of the A549 cells with the diol-epoxides were followed by an alkaline elution procedure. The effect of this treatment on the lengths of the newly synthesized daughter strands and on the total amounts of DNA synthesized was determined as a function of posttreatment incubation. Parental DNA strands were fragmented within the first 3 hr following treatment with either of the diol-epoxides and then slowly elongated to the length of untreated control samples during 30 hr of incubation. The treatment also increased the fraction of short daughter strands within the first 3 hr of incubation. This fraction returned to control levels after 15 hr of incubation. Both diol-epoxides exerted similar effects on the integrity of parental DNA and on daughter strand synthesis. The total amount of DNA synthesized within a 30-min period decreased to 10%-25% of that synthesized by untreated control cultures during 30 hr of incubation. The results illustrate the repairability of BP-induced DNA damage in human lung cells that are related to the target tissues of polycyclic aromatic hydrocarbon carcinogenesis in humans. (32 refs)

78-5010 **Binding of Benzo(a)pyrene Metabolites to Cellular DNA in Perfused Rat Lungs.** (Eng) Deckers-Schmelzle, B. (Pharmakologisches Institut, Universitat Mainz, Obere Zahlbacher Strasse 67, D-6500 Mainz, W. Germany); Klaus, E.; Kahl, R.; Kahl, G. F. *Naunyn Schmiedebergs Arch Pharmacol* 303(3): 303-307; 1978.

The influence of pretreatment with the monooxygenase inducers β-naphthoflavone (NF) and phenobarbitol (PB) on total irreversible binding of metabolically activated ^{3}H-benzo(a)pyrene (BP) to cellular DNA and the formation of DNA nucleoside-BP adducts after cytochrome P-448 induction was studied in isolated perfused lungs of male Sprague-Dawley rats. Pretreatment with PB (80 mg/kg x 3, ip) increased binding only slightly, but pretreatment with NF (80 mg/kg ip) increased binding by a factor of 23 [7 picomoles (pmol) of BP equivalents/lung bound to DNA vs 0.3 pmol in controls]. In the lungs of NF-induced rats, 0.45, 2.46, and 7.61 pmol of BP equivalents/mg were bound in the DNA, RNA, and protein fractions, respectively. The corresponding control values were 0.02, 0.12, and 0.50 pmol. The two major nucleoside adducts were partially identified by Sephadex LH-20 chromatography of hydrolyzed DNA of lungs from NF-treated rats. These adducts were ascribed to modification of the DNA with a BP 7,8-dihydrodiol-9,10-epoxide and with secondary metabolites of BP phenols. (31 refs.)

78-5011 **Ellipticines as Potent Inhibitors of Aryl Hydrocarbon Hydroxylase: Their Binding to Microsomal Cytochromes P450 and Protective Effect Against Benzo(a)pyrene Mutagenicity.** (Eng) Lesca, P. (Laboratoire de Pharmacologie et Toxicologie Fondamentales, 205 route de Narbonne, 21078 Toulouse Cedex, France); Lecointe, P.; Paoletti, C.; Mansuy, D. *Biochem Pharmacol* 27(8): 1203-1209; 1978.

The interaction of ellipticine (4,11-dimethyl-6-H-pyrido(4,3b)carbazole) and several of its derivatives with rat liver cytochromes P450 was studied. Wistar rats were inoculated ip with phenobarbital (PB: 80 mg/kg/day for 3 days), benzo(a)pyrene (BP: 20 mg/kg/day for 2 days), ellipticine (20 mg/kg/day for 2 days), or Aroclor 1254 (500 mg/kg, one dose 5 days before sacrifice). All the ellipticine derivatives produced the same type of difference spectrum with a peak of 428 nanometers (nm) using oxidized hepatic microsomes and at 445 nm using dithionite-reduced microsomes (spectral dissociation constants of 10^{-6} and 10^{-5} M, respectively). Ellipticine was a better inhibitor of microsomal BP hydroxylase than 7,8-benzoflavone or metyrapone, regardless of the type of induction. This is attributed to the high affinity of ellipticine for microsomal cytochrome P448. Very low ellipticine concentrations (2.3 x 10^{-6} M-7.5 x 10^{-6} M) inhibited the covalent binding of BP to DNA by 50%. The efficiency of the inhibitor was high whatever the source of the microsomes, the smallest effect being obtained with PB-induced microsomes. Ellipticine and 9-hydroxyellipticine inhibited the mutagenicity of BP for *Salmonella typhimurium* TA100 by 60% and 78%, respectively, when BP and ellipticine concentrations were equal. Ellipticine (and, to a lesser extent, 9-hydroxyellipticine) was mutagenic by itself. The hypothesis that ellipticines might inhibit the microsome-dependent mutagenicity of many chemicals is under investigation. (34 refs)

78-5012 **Glutathione S-Transferase Activities in Rat and Mouse Sperm and Human Semen.** (Eng) Mukhtar, H. (Lab. Pharmacology, Natl. Inst. Environmental Health Sciences, PO Box 12233, Research Triangle Park, NC, 27709); Lee, I. P.; Bend, J. R. *Biochem Biophys Res Commun* 83(3): 1093-1098; 1978.

Glutathione S-transferase activity was found in the sperm of Sprague-Dawley rats and DBA/2J and C57BL/6J mice and in human semen with the use of benzo(a)pyrene 4,5-oxide (4,5-BPO), styrene 7,8-oxide (SO), or 1-chloro-2,4-dinitrobenzene (CDNB) as substrates. Specific rat sperm activities with 4,5-BPO, SO, and CDNB were 0.88, 1.07, and 26. nanomoles (nmol)/min/mg protein, respectively. These values represent 1.9%, 0.4%, and 1.4% of the specific hepatic cytosol activities in the rat. The specific Δ^5-3-ketosteroid isomerase activity in sonicated rat sperm was 2.46 nmol/min/mg protein, representing 4.1% of the hepatic cytosol activity. Mouse sperm activities were similar to those in rat with 4,5-BPO as substrate and slightly higher with CDNB as substrate. Semen from four healthy individuals had significant glutathione S-transferase activity, ranging from 47 to 112 nmol/min/ml ejaculate and from 1.0 to 3. nmol/min/ml ejaculate, respectively, with CDNB and 4,5-BPO as substrates. The presence of glutathione S-transferase activity in human semen suggests that it may assist in the detoxification of electrophilic metabolites of environmental chemicals. (23 refs.)

78-5013 **Epoxide Hydrase Activity in Liver Nuclei: Hydration of Benzo(a)pyrene-4,5-oxide and Styrene Oxide.** (Eng) Bornstein, W. A. (Dept. Cell and Molecular Biology, Medical Coll. Georgia, Augusta, GA); Chuang H.; Bresnick, E.; Mukhtar, H.; Bend, J. R. *Chem Biol Interac* 21(2/3): 343-346; 1978.

The presence of epoxide hydrase activity in purified nuclei isolated from the livers of male Sprague-Dawley rats was determined by high-pressure liquid chromatography (HPLC) and by a radioactive assay with the use, at least in one case, of two different substrates. For the HPLC assay, the incubation system (total volume, 0.8 ml) consisted of nuclei (up to 10 mg protein in 0.25 M sucrose), Na phosphate buffer [pH 8.0, 60 micromoles (μmol)], and benzo(a)pyrene 4,5-oxide [BP 4,5-oxide, 185 nanomoles (nmol)]. The radioactive assay was conducted in a 0.2-ml incubation mixture of nuclei, HEPES buffer (pH 9.0, 25 μmol), 7-^{3}H-styrene oxide (20

nol) or ^{3}H-BP 4,5-oxide (9 nmol), and water. In the HPLC say, enzyme activity was directly proportional to nuclear otein (up to 10 mg) and to time (to 20 min). In the radioace assay, linearity was observed for both styrene oxide (up 3 mg nuclear protein and 10 min of incubation) and BP -oxide (up to 1 mg protein and 15 min of incubation). With 4,5-oxide, the specific activity by either assay was 3-0.35 nmol/min/mg protein; with styrene oxide, the spe- ic activity was 0.41 nmol/min/mg. Under identical condi- ns and with BP 4,5-oxide as substrate, the enzyme activity liver microsomes was approx 25 times this level. It is sug- sted that the nucleus becomes not only a prime target for e action of polycyclic hydrocarbons, but that it may also present the means by which these substances are metaboli- lly activated for mutagenesis, teratogenesis, or carcino- nesis. (6 refs.)

-5014 **Changes in Peroxidation During Benzo(a)pyrene-induced Carcinogenesis.** (Rus) Lankin, V. (Inst. Chemical Physics, USSR Academy of Sciences, oscow, USSR); Gerasimov, A. M.; Poliakov, V. M.; proleva, L. A.; Antonenkov, V. D.; Gurevich, S. M. *Biokmiia* 43(2): 235-239; 1978.

ne effect of benzo(a)pyrene (BP) on the intensity of peroxide etabolism in the liver was studied in random-bred albino ts. The animals received a single injection of BP (5 mg, sc) d, 3-3.5 mo later, when they developed tumors (pleomorphic cell sarcoma), they were sacrificed. The amount of tal lipids in the liver tissue of the tumor-bearers was 15.2 g/g, compared with 43.7 mg/g in the liver of control anials. Tumorigenesis resulted in a significant decrease of catase and urate oxidase activities (2x and 1.5x, respectively), 29% decrease of glutathione reductase activity, a 142% crease of glutathione peroxidase activity, and a 12% inease of the activity of the NADPH-dependent system of crosomal phospholipids peroxidation. The amount of lipid roxides in the liver of the tumor-bearers was 23.4 nomoles/mg, compared with 11.2 nanomoles/mg controls. (23 refs)

-5015 **Co-Oxygenation of Chemicals (Benzopyrene) During Prostaglandin Biosynthesis (Meeting stract).** (Eng) Sivarajah, K. (Pharmacokinetics Section, b. Pharmacology, NIEHS, Research Triangle Park, NC, 709); Anderson, M.; Eling, T. *Environ Health Perspect* 20: 3-234; 1977. (no refs)

-5016 **Effect of Dietary Phenobarbital, 3,4-Benzo(a)pyrene and 3-Methylcholanthrene on Hepatic, testinal, and Renal Glutathione S-Transferase Activities the Rat.** (Eng) Clifton, G. (Clinical Investigation Center, ival Regional Medical Center, Oakland, CA, 94627); Kaowitz, N. *Biochem Pharmacol* 27(8): 1284-1287; 1978.

The effect of dietary phenobarbital (PB), 3,4-benzo(a)pyrene (BP), and 3-methylcholanthrene (MCA) (40 mg/kg/day for 14 days) on hepatic, intestinal, and renal glutathione S-transferase activities was studied in male Sprague-Dawley rats. Significant increases in hepatic transferase activities for the following substrates were observed in the PB-treated animals vs controls: 3,4-dichloronitrobenzene (DCNB; 102%), 1-chloro-2,4-dinitrobenzene (CDNB; 145%), p-nitrobenzyl chloride (NBC; 111%), 1,2-epoxy-3-(p-nitrophenoxy)propane (31%), and ethacrynic acid (EA; 51%). BP increased hepatic activity for all substrates except CDNB; MCA had no effect on activity of the epoxide. In the intestine, PB increased transferase activity of DCNB, CDNB and NBC; BP increased activity for EA and the epoxide; and MCA increased activity for CDNB only. In the kidney, MCA increased transferase activity for DCNB, CDNB, NBC and EA. Dietary PB and BP had no inductive effects in the kidney. The PB induction in the liver and small intestine was significantly greater for activity with DCNB, CDNB, and NBC, as opposed to activity with the epoxide or EA. This difference in degree of induction was not seen with BP or MCA and suggests a greater induction of certain transferases by PB. These results differ from those of a study in which the substances were administered parenterally, which indicates that the administration route plays an important role in glutathione S-transferases induction. (24 refs.)

78-5017 **Synthesis of the Non-K-region and K-Region trans-Dihydrodiols of Benzo(e)pyrene.** (Eng) Lehr, R. E. (Dept. Chemistry, Univ. Oklahoma, Normal, OK, 73019); Taylor, C. W.; Kumar, S.; Mah, H. D.; Jerina, D. M. *J Org Chem* 43(18): 3462-3466; 1978.

Experimental procedures for the synthesis of trans-9,10-dihydroxy-9,10-dihydrobenzo(e)pyrene and trans-4,5-dihydroxy-4,5-dihydrobenzo(e)pyrene are described. The former was synthesized with an overall yield of 50% to 60%, and the latter was obtained in a quantitative yield. (22 refs.)

78-5018 **Metabolism of Benzo[a]pyrene and Benzo[a]pyrene 4,5-Oxide by the Isolated Perfused Rabbit Lung (Meeting Abstract).** (Eng) Smith, B. R. (Pharmacology and Biomedicine Section, Lab. Pharmacology, NIEHS, Research Triangle Park, NC, 27709); Bend, J. R. *Environ Health Perspect* 20: 230; 1977. (no refs)

78-5019 **Inability of Vitamin A Deficiency to Alter Benzo(a)pyrene Metabolism in Syrian Hamsters.** (Eng) Bornstein, W. A. (Dept. Biochemistry, Univ. Vermont Coll. Medicine, Burlington, VT, 05401); Lamden, M. P.; Chuang, A. H.; Gross, R. L.; Newberne, P. M.; Bresnick, E. *Cancer Res* 38(6): 1497-1501; 1978.

The effect of vitamin A deficiency on the in vitro metabolism of benzo(a)pyrene (BP) was investigated. Male Syrian golden hamsters were placed either on a control or vitamin A-deficient diet, and when the serum vitamin A levels of the latter were reduced to $<10\%$ of the former, the hamsters were decapitated and lung aryl hydrocarbon hydroxylase activity and BP metabolism were measured. Slightly greater aryl hydrocarbon hydroxylase activity was found in hepatic microsomes from vitamin A-deficient animals, but this difference was not significant. The BP metabolic profile of pulmonary microsomes was similar for control and vitamin A-deficient systems, and only a few quantitative differences were noted. The addition of a vitamin A analog, β-retinyl acetate, to the in vitro incubations did not substantially affect BP metabolism. (47 refs)

78-5020 **Human Pulmonary Alveolar Macrophages Metabolise Benzo(a)pyrene to Proximate and Ultimate Mutagens.** (Eng) Harris, C. C. (Human Tissue Studies Section, Experimental Pathology Branch, Carcinogenesis Res. Program, NCI, Bethesda, MD, 20014); Hsu, I. C.; Stoner, G. D.; Trump, B. F.; Selkirk, J. K. *Nature* 272(5654): 633-634; 1978.

The metabolic activation of benzo(a)pyrene (BP) by human pulmonary alveolar macrophages (PAM) into a promutagen, (±)r7,t8-dihydroxy-7,8-dihydrobenzo(a)pyrene (7,8-diol; 50% +), and an ultimate mutagen was investigated in a cell-mediated mutagenesis system using Chinese hamster V-79 cells as the indicator cells. The mutation frequency for ouabain resistance was directly dependent on the number of PAM added to the V-79 cells in medium containing either BP or 7,8-diol. Benzo(e)pyrene [B(e)P], the noncarcinogenic analog of BP, was not mutagenic. Cocultivation of V-79 cells with PAM but without BP, B(e)P, or 7,8-diol did not alter the spontaneous mutation frequency. An increase in concentration of either BP or 7,8-diol enhanced mutation frequencies. Compared with BP, 7,8-diol was a more potent promutagen. PAM also metabolized BP to 7,8-diol, which was released by PAM into the culture medium. These data suggest that PAM can metabolize BP to proximate and ultimate mutagens, which are then released into the extracellular space. The intimate contact between PAM and bronchial epithelium during clearance by the mucociliary transport system of particulates containing chemical carcinogens within PAM suggests the possibility that PAM and bronchial epithelium may act in concert to metabolically activate chemical carcinogens during bronchogenic carcinogenesis. (13 refs.)

78-5021 **Binding of the Carcinogens Benzo(a)pyrene (BP) and 7,12-Dimethylbenz(a)anthracene (DMBA) to Salmonella DNA as Compared to the Corresponding Mutagenicity (Meeting Abstract).** (Eng) Manthey, B. (Inst. Toxicology, ETH/Univ. Zurich, CH-8603 Schwerzenbach, Switzerland); Lutz, W. K.; L'Eplattenier, E.; Schlatter, C.; Wurgler, F. *Experientia* 34(7): 927; 1978. (no refs)

78-5022 **Evidence That Benzo(a)anthracene 3,4-Diol-1,2-Epoxide Is an Ultimate Carcinogen on Mouse Skin.** (Eng) Levin, W. (Dept. Biochemistry and Drug Metabolism, Hoffmann-LaRoche Inc., Nutley, NJ 07110); Thakker, D. R.; Wood, A. W.; Chang, R. L.; Lehr R. E.; Jerina, D. M.; Conney, A. H. *Cancer Res* 38(6) 1705-1710; 1978.

Benz(a)anthracene (BA) and several benzo ring derivative of BA were examined for their tumor-initiating activity fol lowing topical applications of 0.1-2.0 micromoles to the ski of female CD-1 mice, followed 7 days later by twice weekl applications of 12-O-tetradecanoylphorbol-13-acetate for 2 wk. Comparisons of the percentage of mice with papilloma and the number of papillomas per mouse indicated that both diastereomeric 3,4-dihydroxy-1,2-epoxy-1,2,3,4-tetrahy droBA's (DETBA's), in which the epoxide oxygen is eithe cis (diol-epoxide 1) or trans (diol-epoxide 2) to the benzyli 4-hydroxyl group, were 10 to 40 times more tumorigenic tha BA. Diol-epoxide 2 was two- to threefold more tumorigeni than diol-epoxide 1 after 20 wk of promotion. The immediat metabolic precursor of the DETBAs, trans-3,4-dihy droxy-3,4-dihydroBA, had intermediate activity compared t diol-epoxides 1 and 2 and was approx 20 times more tumori genic than BA. Resolution of the racemic trans-3,4-dihy droxy-3,4-dihydroBA into the (-)-/and (+)-enantiomers an assignment of their absolute stereochemistry revealed that th (-)-(3R,4R) isomer was at least fivefold more active as a tu mor initiator than the (+)-(3S,4S) isomer. Testing c 1,2-dihydrobenz(a)anthracene and 3,4-dihydrobenz(a)an thracene for carcinogenicity revealed the latter to be the mos potent compound used in this study; the former had activit comparable to that of BA. These findings suggest that a di ol-epoxide in which the epoxide on a saturated, angular benz ring forms part of a 'bay region' of the hydrocarbon is a prim candidate for an ultimate carcinogenic metabolite of the hy drocarbon. For BA, this metabolite is either or both of th diastereomeric DETBA's. (39 refs)

78-5023 **Formation of Glucuronic Acid Conjugates 7,12-Dimethylbenz(a)anthracene Phenols i 7,12-Dimethylbenz(a)anthracene-treated Hamster Embry Cell Cultures.** (Eng) Baird, W. M. (Wistar Inst. Anatom and Biology, 36th St. at Spruce, Philadelphia, PA, 19104 Chemerys, R.; Chern, C. J.; Diamond, L. *Cancer Res* 38(10 3432-3437; 1978.

The formation of glucuronic acid conjugates of 7,12-dim thylbenz(a)anthracene (DMBA) phenols in first- or s cond-passage Syrian hamster embryo cells treated with 0 nanomole/ml ^{3}H-DMBA was studied. The cultures metabo ized >90% of the DMBA within 48 hr. Samples of the med um were extracted with chloroform, methanol, and wate The chloroform phases contained about one-third of th DMBA metabolites; the major chloroform-extractab metabolite was 8,9-dihydro-8,9-dihydroxy-DMBA. A Glucuronidase treatment of the aqueous methanol-solub

abolites converted almost 50% of them to chloro-n-soluble metabolites, of which > 80% were identified as nolic derivatives of DMBA. Similar metabolite profiles e obtained by treating the medium with β-glucuronidase re chloroform extraction. Separation of the methyl ıp-hydroxylated derivatives of DMBA from the phenolic vatives was accomplished by high-pressure liquid matography. Small amounts of hydroxymethyl deriva- were detected only in the chloroform-extractable erial, but DMBA phenols were the major component of β-glucuronidase-released material. These results indicate the major pathway of DMBA metabolism in hamster ryo cells is oxidation of the aromatic rings and not oxida- of the methyl groups. (45 refs.)

5024 **In Vitro Development of Oncogenicity in Cell Lines Established from Tracheal Epithelium xposed In Vivo to 7,12-Dimethylbenz(a)anthracene.** g) Marchok, A. C. (Biology Div., Oak Ridge Natl. Lab., Box Y, Oak Ridge, TN, 37830); Rhoton, J. C.; Nette-n, P. *Cancer Res* 38(7): 2030-2037; 1978.

nsplanted rat tracheas were exposed to 150 or 650 μg -dimethylbenz(a)anthracene (DMBA) over a 2-wk peri-nd epithelial cell lines derived from these tracheas were d periodically in vivo for development of oncogenicity for phenotypic changes associated with neoplastic trans-nation in vitro. Among three cell lines obtained from tra-s preexposed to 150 μg DMBA, tumorigenicity was onstrated only in the late passages of two cell lines main-ed to 400 days or more in vitro. With these cells, in vivo or latency was 115-255 days. Eight of nine cell lines ved from tracheas preexposed to 640 μg DMBA became origenic. Several were oncogenic after approx 200 days tro, and they yielded palpable tumors within 9-80 days inoculation. In several instances, inoculation of cells an early passage into immunosuppressed isogeneic pients resulted in the development of keratinic cysts or ors that regressed. Inoculation of later passages of the e cell lines resulted in the development of invasive tu-s. Loss of anchorage dependence of growth was, in most s, a reliable phenotypic marker for the development of genicity, as was colony-forming efficiency on plastic. All e cell lines were epithelial, as indicated by ultrastructural acteristics, the production of keratin in vitro, and/or the nation of squamous cell carcinomas upon inoculation in . The cell lines had stable morphological characteristics nguishing each cell line from any other by growth pat-cell shape, and degree of keratinization. The data indi-that the carcinogenesis initiated in epithelial cells in vivo inues in culture. Thus, it should be possible to study in il both the evolution of neoplasia and factors affecting rogression. (32 refs)

5025 **Biological Influence of Fat Intake on Mammary Cancer and Mammary Tissue: Experimental Correlates.** (Eng) Nishizuka, Y. (Lab. Experimental Pathology, Aichi Cancer Center Res. Inst., Chikusa-ku, Nagoya 464, Japan). *Prev Med* 7(2): 218-224; 1978.

The effect of dietary fat on 7,12-dimethylbenz(a)anthracene (DMBA)-induced tumors was investigated in Sprague-Dawley rats. Following two iv injections of DMBA at 8 wk of age, the rats were given similar amounts of four different semisynthetic, isocaloric fat diets (8% and 20% coconut oil and corn oil diets) for 8 wk starting at 12 wk of age. At the end of this period, they were placed on the control diet. The induced mammary carcinoma and mammary fat pads were examined at 2-to 3-wk intervals for 13 wk after return to the control diet. Fatty acid compositions in both tissues reflected those of the diets ingested; this finding was more obvious in the high-fat groups. In the cancer tissues, polyunsaturated fatty acids were detected in larger amounts. The uptake of tritiated thymidine appeared to be increased in both tissues of rats fed the high-fat diet. The fatty acid patterns in neoplastic tissue, especially that of lauric acid in the coconut oil group, remained for a longer period of time after return to the control diet. These findings suggest that the promoting influence of a high-fat diet on chemical-induced mammary carcinomas is related to the retention of dietary fats in the adipose tissue and their slower turnover in cancer tissues. The literature data on the association between diet and mammary carcinogenesis are reviewed. (21 refs)

78-5026 **Studies on the Mechanism of Neuro-Oncogenesis by Polycyclic Aromatic Hydrocarbons (Meeting Abstract).** (Eng) Kleihues, P. (Abteilung Neuropathologie, Pathologisches Institut der Universitat Freiburg, 78 Freiburg, W. Germany). *J Neuropathol Exp Neurol* 37(5): 643; 1978. (no refs)

78-5027 **Indirect Chromosomal Fluorescence with Antibody to 7,12-Dimethylbenz(a)anthracene.** (Eng) Balick, R. (The Ben May Lab. Cancer Research, Univ. Chicago, Chicago, IL, 60637); Pataki, J. *Biochem Biophys Res Commun* 82(1): 81-84; 1978.

An indirect immunofluorescence technique was applied to acid-alcohol fixed metaphase chromosome preparations from rats treated with 7,12-dimethylbenz(a)anthracene in order to study the mechanism of polycylic aromatic hydrocarbon (PAH) carcinogenesis. Numerous binding modalities were observed reflecting the extent of chromosomal modification. Isolation of chromatin derived from specific chromosomes would further facilitate research concerning the chemical nature of PAH carcinogenesis. (10 refs)

78-5028 **Neoplasia Following Cessation of DMBA Application to Hamster Buccal Pouch.** (Eng) Eisenberg, E. (Dept. Oral Medicine and Oral Pathology, Har-

vard Sch. Dental Medicine, Boston, MA, 02115). *J Dent Res* 56(11): 1430; 1977.

9,10-Dimethyl-1,2-benzanthracene (DMBA: 0.5% soln) was applied 3x/wk for 8-10 wk to the buccal pouch of Syrian golden hamsters. In 100% of the animals, the dysplasia that was induced resulted in carcinoma, without the continuous application of DMBA after week 10. This progression of dysplasia to frank neoplasia is predictable, and it obviates the need for continuous application of carcinogen. (no refs)

78-5029 **Restraint-induced Inhibition of 7,12-Dimethylbenz[a]anthracene-induced Mammary Tumors: Relation to Stages of Tumor Development.** (Eng) Newberry, B. H. (Dept. Psychology, Kent State Univ., Kent, OH, 44242). *J Natl Cancer Inst* 61(3): 725-729; 1978.

Experiments were conducted on the use of chronically applied restraint to reduce the number of mammary tumors developing in response to treatment of Sprague-Dawley rats with 7,12-dimethylbenz[a]anthracene (5 mg/g iv at 50, 53, and 56 days of age; total dose, 6 mg). Restraint was applied by inserting animals in hardware cloth tubes that did not allow reversal of the facing direction. The restraint duration was 12 or 14 hr/day in the light portion of the light-dark cycle. The results indicated that the inhibitory effect was largely due to restraint applied after the induction period; preinduction restraint and induction period restraint had no significant effect on tumor development. Therefore, to a considerable extent at least, the restraint effect seems due to an interference with the proliferation of neoplastic cells. After termination of the restraint treatment, the rate at which new tumors appeared first increased and then decreased. Restraint did not affect the proportion of tumors regressing after ovariectomy. (19 refs.)

78-5030 **Bacillus of Calmette and Guerin and 7,12-Dimethylbenz(α)anthracene Carcinogenesis in Mice.** (Eng) Scelsi, R. (Istituto di Anatomia e Istologia Patologica, Via Forlanini 14-18, 27100 Pavia, Italy); Scelsi, M.; Poggi, P.; Mosca, L. *Gastroenterol Clin Biol* 64(4): 353-360; 1978.

The effects of single and repeated treatments with BCG on 7,12-dimethylbenz(a)anthracene (DMBA)-induced tumorigenesis were studied in Swiss mice. A total of 500 mice were given a single sc injection of DMBA (100 θg) within 16 hr of birth. Of this number, 100 animals received a single sc injection of BCG (1 x 10^7 cells suspended in 0.2 ml saline) at 20 days and 400 received multiple injections (up to 5) at intervals from 20 to 140 days after birth. All animals were sacrificed at 250 days of age. Among the animals treated with DMBA alone, there were 14 lung adenomas, 11 thymic lymphomas, 3 sc sarcomas, 1 liver hemangioma, 1 mammary adenocarcinoma, and 1 ovarian cystoma. Animals that received two or more doses of BCG had a lower tumor incidence than untreated animals or those given only one dos Reduction in tumor incidence was correlated with length c BCG treatment. Malignant thymic lymphomas were particu larly sensitive to the action of BCG, none developed in an mals receiving multiple injection. BCG should be able to alte the action of carcinogens by its effect on the reticuloendo thelial system and enzyme levels. (26 refs.)

78-5031 **The Preparation of Dihydrodiols from 7-Me thylbenz(a)anthracene.** (Eng) Tierney, B. (Che ter Beatty Res. Inst., Inst. Cancer Res., Royal Cancer Hosp Fulham Road, London SW3 6JB, England); Abercrombi B.; Walsh, C.; Hewer, A.; Grover, P. L.; Sims, P. *Chem Bi Interact* 21(2/3): 289-298; 1978.

7-Methylbenz(a)anthracene (MBA) was oxidized by an a corbic acid-ferrous sulfate mixture, and 3/5 trans-dihydrod ols (DHD) formed were isolated, purified, and characterize MBA (1 g) dissolved in 3 liters of acetone was divided amon four flasks, each containing ascorbic acid (40 g), EDTA (2. g), and ferrous sulfate (5.0 g) dissolved in 750 ml water, an the reaction was allowed to proceed for 18 hr. The thre non-K region DHD (trans-1,2-dihydro-1,2-dihydroxy-MBA trans-3,4-dihydro-3,4-dihydroxy-MBA, and trans-8,9-dihy dro-8,9-dihydroxy-MBA) were obtained in acceptable quan tities, but only trace amounts of the 5,6- and 10,11-DH were formed. The non-K region DHD were purified b thin-layer chromatography followed by preparativ high-pressure liquid chromatography. The UV spectra of th non-K region DHD were similar to those of the correspon ing non-K region DHD derived from benz(a)anthracene, e cept that, in the former, the peaks were shifted by 2 nanometers to longer wavelengths. The methyl grou adjacent to the aromatic system probably caused th shift. The mass spectra of the three DHD confirme the proposed mol wt and showed a strong parent io peak at m/e 276. Both the 1,2- and 8,9-DHD had simil nuclear magnetic resonance (NMR) spectra, excep that the chemical shift for H(1) of the 1,2-DHD w downfield of values typical of benzylic-type carbin protons and was indicative of a bay region DH group. In the 8,9-DHD, the hydroxyl groups preferred to b in a quasi-diaxial conformation, giving rise to a low couplin constant. Additional evidence for the trans-configuration o the hydroxyl groups of 8,9-DHD was provided by the ident ty of the NMR spectrum of the compound prepared by oxida tion to that of the compound prepared by metabolism o MBA in a rat liver homogenate. The NMR spectrum o 3,4-DHD gave a large coupling constant between H(3) an H(4), typical of a trans-DHD in which a quasi-diequatoria conformation is preferred. (26 refs.)

78-5032 **Carcinogenic Polycyclic Aromatic Hydroca bons and Their Metabolites as Possible Emi sion Components.** (Ger) Herlan, A. (Karlsruhe, W. Ge many). *Reinhalt Luft* 38(7): 276-278; 1978.

l oils, highway dusts, and oil furnace emissions were sam- l for carcinogenic aromatic polycyclic hydrocarbons. The ıples contained 200-500 aromatic compounds. Coronene, ene epoxide, phenol, cresol, pyrene, anthantriol, epoxyan- ıcene, epoxymethanophenanthrene, epoxypyrene, and xybenzopyrene were among the carcinogenic hydrocar- s identified. (no refs.)

5033 **Binding of Dibenzo(a,e)fluoranthene, a Carcinogenic, Polycyclic Hydrocarbon Without K-Re- ı, to Nucleic Acids in a Subcellular Microsomal System.** g) Perin-Roussel, O. (Laboratoire de Chimie des Sub- ıces Naturelles, C.N.R.S., 91190 Gif-sur-Yvette, France); rt, B.; Zajdela, F.; Jacquignon, P. *Cancer Res* 38(10): 9-3504; 1978.

imal conditions were determined for the binding of libenzo(a,e)fluoranthene (DBF), a carcinogenic polycy- hydrocarbon without an apparent K-region, to nucleic s when incubated with hepatic microsomal fractions. Me- cholanthrene-pretreated mouse liver microsomes induced gher level of binding of DBF to DNA than did similarly ıced rat liver microsomes. 7,8-Benzoflavone strongly in- ted the binding of this polycyclic aromatic hydrocarbon)NA, but cyclohexene oxide and trichloropropene oxide an enhancing effect when used in the presence of rat liver rosomes. An inhibitory effect was also observed with cy- exene oxide in mouse liver microsome-enriched medium. eled DBF bound twice as much to denatured as to native A. Incubation of DBF in the presence of liver microsomes polyribonucleotides (polyadenylate, polyuridylate, guanylate, and polyinosinate) indicated that binding oc- mainly with guanine. Binding of DBF to DNA of vari- origins was directly proportional to the amount of gua- -cytosine pairs. Preliminary results indicate that there is valent bond between DBF and nucleic acids. (45 refs.)

5034 **A Novel and Convenient Synthesis of Dibenz- [a,c]anthracene.** (Eng) Harvey, R. G. (Ben May . Cancer Res., Univ. Chicago, Chicago, IL, 60637); ba, C.; Konieczny, M.; Fu, P. P.; Sukumaran, K. B. *J Org m* 43(17): 3423-3425; 1978.

mple method for the synthesis of dibenz(a,c)anthracene A) is presented. The method involves direct reductive ization of 2-(9′-phenanthroyl)benzoic acid to DBA with roiodic acid in refluxing acetic acid. There was a 90% l of DBA. (9 refs.)

5035 **Synthesis of Aryloxiranes.** (Eng) Yang, N. C. (Dept. Chemistry, Univ. Chicago, Chicago, IL, 7); Chiang, W.; Leonov, D.; Leonov, E.; Bilyk, I.; Kim, *Org Chem* 43(17): 3425-3427; 1978.

Three experimental procedures for the synthesis of 1-pyrenyl-, 9-anthryl-, 1-naphthyl-, 2-naphthyl-, 7-benzanthryl-, 6-chrysenyl-, 10-methyl-9-anthryl-, 9-phenanthryl-, and 9,10-dimethyl-2-anthryloxirane and 9,10-bis(oxiranylanthracene) are presented. The yields of these compounds ranged from 69% to 94%. The compounds may be used as models for the activated forms of polynuclear hydrocarbons. (14 refs.)

78-5036 **Tumor Persistence and Regression in Skin Carcinogenesis. An Experimental Study.** (Eng) Stenback, F. (Dept. Pathology, Univ. Oulu, Kajaanintie 52 D, SF 90220 Oulu 22, Finland). *Z Krebsforsch* 91(3): 249-259; 1978.

The incidence of skin tumors and factors in the regression and progression of these tumors were determined in 600 female Swiss mice treated topically with 7,12-dimethylbenz-(a)anthracene (DMBA) and/or 12-O-tetradecanoylphorbol-13-acetate (TPA). The animals were divided into five groups: Group 1 received a single application of 300 μg DMBA; Group 2, DMBA followed by 3.2 μg TPA 2x/wk for 15 wk; Group 3, 30 μg DMBA and TPA; Group 4, 5 μg DMBA 1x/wk for life; Group 5, untreated controls. Groups 1-3 developed a large number of skin tumors, many of which regressed spontaneously. Most of the tumors were papillomas, although keratoacanthomas and squamous cell carcinomas were observed in small numbers. Max tumor incidence and tumor regression in these groups occurred early in the experiment, with the number of developing and regressing tumors following a cyclical pattern. In Group 4 mice, tumors occurred in almost all animals and the incidence of regression was low; in contrast to Groups 1-3, it occurred mainly in tumors lasting >3 wk. There was a definite correlation between type of treatment and regression: in Group 4, only 1/37 tumors lasting ≤ 3 wk regressed but in Group 3, only 1/16 tumors lasting ≤ 3 wk persisted. Regression was associated to a limited extent with tumor size, tumor duration, and total number of tumors. Histological disorganization, ie, disturbed stratification and polarization, cytological irregularities, nuclear hyperchromatism, and cellular enlargement, was consistent with prolonged tumor duration. The results indicate that neoplastic transformation occurs in multiple stages (hyperplastic lesions, benign regressing tumors, persistent tumors, and frankly malignant tumors), with the incidence and biclogical behavior of the tumors depending on treatment. (24 refs)

78-5037 **The Role of the Induction of Ornithine Decarboxylase in Tumor Promotion.** (Eng) Boutwell, R. K. (McArdle Lab. Cancer Res., Univ. Wisconsin Medical Center, Madison, WI, 53706). *In: Mechanisms of Carcinogenesis. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor

Laboratory): Origins of Human Cancer. Vol. 4 (Book B), 699 pp.; 773-783; 1977.

Evidence supporting the induction of ornithine decarboxylase (OD) as a phenotypic change specific and essential for skin tumor formation is presented. The tumor-promoting activity of phorbol esters has been linked to the induction of OD and S-adenosylmethionine decarboxylase (SAMD). The latter, but not the former, is also induced by nonpromoting irritants such as acetic acid and cantharidin. Promoting activity is achieved only when the carcinogens are applied in excess of certain threshold levels; below these levels, promoting activity is lost and only initiation occurs. Skin tumors contain increased levels of OD but not of SAMD. It is suggested that normal tissue possesses an efficient system for the inactivation of OD and that treatment with a carcinogen results in a loss of this capacity, a loss that becomes permanent after several treatments with promoter levels of the compound. Data suggest that neither cyclic AMP nor cyclic guanosine monophosphate acts as a second messenger in the induction of OD by the tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA). Colchicine-sensitive structures may serve in the transmission into the interior of the cell of signals resulting from TPA contact with the cell membrane. Mice pretreated with retinoic acid, an inhibitor of tumor formation, showed only a small increase in OD in response to TPA treatment; the induction of SAMD activity was not altered in these animals. (22 refs.)

78-5038 **Metabolism of Tritium-labeled 12-O-Tetradecanoylphorbol-13-acetate by Cells in Culture.** (Eng) O'Brien, T. G. (Wistar Inst. Anatomy and Biology, Philadelphia, PA, 19104); Diamond, L. *Cancer Res* 38(8): 2562-2566; 1978.

The metabolism of tritium-labeled 12-O-tetradecanoylphorbol-13-acetate (^{3}H-TPA) by Syrian hamster embryo fibroblasts (HEF) and by human fibroblasts (line HC-4, from normal conjunctiva of an infant with retinoblastoma) was studied to determine whether the tumor promoter itself or a metabolite is the biologically effective agent. Within 2-3 days after its addition to growing or confluent cultures of HEF, no unchanged ^{3}H-TPA remained in the medium, as determined by thin-layer chromatography of the chloroform phase obtained by extraction of the medium with chloroform:methanol:water. In contrast, little or no metabolism of ^{3}H-TPA occurred in cultures of human fibroblasts. Over 7 days, the radioactivity in the chloroform phase decreased from 99% to only 93% (similar to control flasks containing medium only). The major metabolite formed in the HEF cultures was ^{3}H-phorbol-13-acetate. With both cell types, 99% of the cell-associated radioactivity was chloroform-extractable, and virtually all was unchanged ^{3}H-TPA, although a minor peak of radioactivity did migrate with the solvent front of the chromatogram of the chloroform extracts from human cells. It appears that, once metabolism of ^{3}H-TPA occurs, most of the metabolites produced are found in the medium. (23 refs)

78-5039 **Establishment of Epithelial Cell Lines Following Exposure of Cultured Tracheal Epithelium to 12-O-Tetradecanoyl-phorbol-13-acetate.** (Eng) Steel, V. E. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830); Marchok, A. C.; Nettesheim, P. *Cancer Res* 38(10): 3563-3565; 1978.

Permanent epithelial cell lines were established from Fischer 344 rat tracheal epithelium following its exposure in vitro to 12-O-tetradecanoyl-phorbol-13-acetate (TPA). Organ cultures were prepared from the tracheas of 12-wk-old rats. Beginning on day 9 of culture, 2- x 3-mm explants were exposed for 1 hr every 6 days to 0, 0.01, or 1.0 μg TPA/ml medium for a total of four or eight exposures. Primary cell cultures derived from 18/20 TPA-exposed explants demonstrated morphologically altered cells after approx 150-180 days. These cells had a markedly higher nuclear to cytoplasmic ratio, and they grew more rapidly across the surface of the dish than did the remainder of the primary or control cells. These cells could be repeatedly subcultured in >95% of the cases. The exposure mode that gave the greatest number of cell lines per explant was four exposures to 1 μg/ml TPA. Fourteen of the cell lines were inoculated into isogeneic animals immunosuppressed by thymectomy and x-radiation; all were nontumorigenic. (19 refs.)

78-5040 **The Action of Tumor-promoting Agents in Cell Culture.** (Eng) Weinstein, I. B. (Inst. Cancer Res., Columbia Univ., Coll. Physicians and Surgeons, New York, NY, 10032); Wigler, M.; Pietropaolo, C. *In: Mechanisms of Carcinogenesis. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book B), 699 pp.; 751-772; 1977.

The actions of tumor-promoting agents in cell cultures were studied. Extremely low concentrations (10^{-9}M) of 12-O-tetradecanoylphorbol-13-acetate (TPA) and certain other phorbol esters caused a rapid and marked induction of the synthesis of plasminogen activator (PA), a tumor-associated proteolytic enzyme, in human cell and normal chick embryo fibroblast (CEF) cultures. The induction appeared to operate at the level of transcription. Morphologic and biochemical changes mimicking those seen upon transformation with Rous sarcoma virus (RSV) were also seen in TPA-treated CEF, and TPA further potentiated the expression of the transformed phenotype in RSV-infected CEF. However, phorbol ester-treated CEF did not display a complete phenocopy of RSV-transformed CEF. Structure-function studies with a variety of phorbol esters and structurally related diterpene plant toxins showed a good correlation between stru

ıral requirements for PA induction in CEF and tumor pro-ıotion in mouse skin. The data suggest the involvement of common cellular receptor in both processes. (43 refs.)

8-5041 **Interactions Between Adenovirus, a Tumor Promoter, and Chemical Carcinogens in Transfor-ation of Rat Embryo Cell Cultures.** (Eng) Fisher, P. B. nst. Cancer Res., Columbia Univ. Coll. Physicians and Sur-eons, New York, NY, 10032); Weinstein, I. B.; Eisenberg, .; Ginsberg, H. S. *Proc Natl Acad Sci USA* 75(5): 2311-2314; 978.

he effect of 12-O-tetradecanoylphorbol-13-acetate (TPA) n the in vitro transformation of cells isolated from Spra-ue-Dawley rat embryos that had been transformed by a tem-erature-sensitive mutant of adenovirus type 5 (H5ts125) or eated with polycyclic aromatic hydrocarbons prior to trans-rmation was determined. TPA (0.1 μg/ml) enhanced the ansformation of secondary embryo cell cultures by H5ts125 vo- to threefold. In addition, transformed foci appeared ear-er and were larger in cultures grown in the presence of TPA. Vhen TPA was added as long as 7 days after viral infection, ıhancement still resulted. Exposure of the cells to benzo(a)-yrene (0.05-0.5 μg/ml) or 7,12-dimethylbenz(a)anthracene .0125-0.1 μg/ml) 18 hr prior to H5ts125 infection also en-ınced transformation (2 to 4 times). This enhancement was rther augmented two- to threefold when cells were grown TPA after virus infection. Although TPA did not enhance ıe cloning efficiency of normal rat embryo cells, it did en-ınce the cloning efficiency of isolated colonies of adenovi-ıs-transformed cells when these cells were grown alone or ocultured with a 100-fold excess of normal rat embryo cells. ransformation could be enhanced with as little as 30 nano-ams/ml of TPA. This action of TPA appeared to be due its ability to facilitate expression of the transformed state ther than to enhance virus uptake or integration. (29 refs)

8-5042 **Stimulation of $^{86}Rb+$ and ^{32}Pi Movements in 3T3 Cells by Prostaglandins and Phorbol Es-ers.** (Eng) Moroney, J. (New York State Dept. Health, Ros-ell Park Memorial Inst., Buffalo, NY, 14263); Smith, A.; omei, L. D.; Wenner, C. E. *J Cell Physiol* 95(3): 287-294; 978.

he relationship between tetradecanoyl phorbol acetate TPA)-mediated changes in ion transport and alterations in on movements induced by structurally similar prostaglan-ins was investigated with the use of the indicators $^{6}Rb+$ as its chloride salt and inorganic ^{32}P (^{32}Pi) phosphoric acid. Among the earliest changes in-uced by TPA was a significant increase in ^{32}Pi in-orporation within 15 min incubation of the post-onfluent fibroblasts in 10^{-8} to 10^{-6} M TPA. Similarly, ıe active phorbol ester homolog 4-β-OH phorbol didecano-e but not the inactive stereoisomeric 4-α-OH phorbol ıdecanoate stimulated ^{32}Pi incorporation. TPA also stimulated $^{86}Rb+$ influx shortly after administration. Both fluxes were ouabain-sensitive, in accord with the idea that an early effect of TPA is to alter (Na+ + K+)-ATPase activity. Prostaglandin E_1 (10^{-7} to 10^{-6} M) and prostaglandin F-2 α (3×10^{-9} to 10^{-7} M) caused a similar stimulation of $^{86}Rb+$ and ^{32}Pi uptake. The finding that water-soluble prostaglandin F-2α also exhibited stimulator effects indicates that the hormone-induced responses were not mediated by solvent interactions. The similar responses of phorbol esters and prostaglandin derivatives suggest that phorbol esters and prostaglandin derivatives may act at common membrane sites. Since stimulatory effects were observed at discrete times in the logarithmic phase of growth, activation of membrane receptors may be cell-cycle-dependent. (20 refs)

78-5043 **A Tobacco Smoke Inhalation Exposure Device for Rodents.** (Eng) Maddox, W. L. (Oak Ridge Gaseous Diffusion Plant, Oak Ridge, TN, 37830); Creasia, D. A.; Dalbey, W. E.; Guerin, M. R.; Stokely, J. R.; Creasia, D. A.; Kendrick, J. *Arch Environ Health* 33(2): 64-71; 1978.

A system that utilizes a piston pump to generate cigarette smoke under standard conditions was used to expose rodents to diluted smoke (via inhalation) for controlled periods of time. The number of puffs and the total particulate matter and nicotine levels per cigarette differed only slightly from predicted values determined with analytical smoking machines. Chamber concentrations of nicotine, CO, and CO_2 were also similar. (8 refs)

78-5044 **Effect of Smoking on Excretion of Tryptophan Metabolite in Urine--3-Hydroxy Anthranilic Acid.** (Eng) Sulochana, G. (Dept. Biochemistry, Medical Coll., Thanjavur 613 004, India); Arunagiri, R. *Indian J Exp Biol* 16(4): 507-508; 1978.

Twenty smokers smoked five cigarettes within a 45-min period, and changes in their urinary excretion of 3-hydroxyanthranilic acid were determined. The smokers had fasted on the morning of the test and had not smoked for at least 12 hr prior to testing. Compared with pretest values, the excretion of this tryptophan metabolite was significantly increased in all 20 subjects 1 hr after the start of the test. (3 refs.)

78-5045 **Pulmonary Carcinogenesis in Rats Given Implants of Cigarette Smoke Condensate in Beeswax Pellets.** (Eng) Dagle, G. E. (Biology Dept., Battelle Pacific Northwest Labs., Richland, WA, 99352); McDonald, K. E.; Smith, L. G.; Stevens, D. L. *J Natl Cancer Inst* 61(3): 905-910; 1978.

Lungs of inbred OM/NCR and outbred Sprague-Dawley rats were given implants, through a thoracotomy, of pellets of

cigarette smoke condensate (CSC) suspended in a beeswax-tricaprylin vehicle. The pellets contained 1-67 mg CSC. The pellets slowly released material into the surrounding parenchyma, which resulted in a dose-related increased incidence of lung cancer, predominantly invasive and metastasizing epidermoid carcinoma. There was a 42% incidence of pulmonary carcinoma in the highest dosage group, in which approx 1.65 cm^2 bronchiolar epithelium was exposed. This dose (67 mg) is approx equal to only three high-tar cigarettes. Pulmonary carcinoma was also produced with 1 mg CSC (1.87% incidence). Squamous metaplasia associated with the implanted site preceded the appearance of the carcinomas, and it increased in severity with the larger pellets that contained more concentrated CSC. There was no difference in pulmonary carcinoma incidence with the use of CSC containing high or low concentrations of nicotine. The potential values of this bioassay system are discussed. (34 refs.)

78-5046 **Lung-Cancer Risks in the Smoking of Different Tobaccos (Meeting Abstract).** (Eng) Betts, T. E. (Res. Labs., Brompton Hosp., London, England); Elson, L. A. *Br J Cancer* 38(1): 193; 1978. (no refs)

78-5047 **Effect of Glycerol on Local and Systemic Carcinogenicity of Topically Applied Tobacco Condensate.** (Eng) Wilson, J. (Central Toxicology Lab., Imperial Chemical Industries Ltd., Alderley Park, Macclesfield, Cheshire SK10 4TJ, England); Clapp, M. J.; Conning, D. M. *Br J Cancer* 38(2): 250-257; 1978.

The effect of glycerol on the topical carcinogenicity of tobacco condensate was studied in female Alderley Park albino mice. Doses of condensate used were 189 and 94.5 mg/mouse/wk, each alone or with 17.5% or 35% glycerol, the balance being made up from solvent (acetone/water, 80/20, volume/volume). The test solns were applied in a volume of 0.3 ml 3 days/wk to the shaved back skin of the mice. Age-standardized results show that in high-condensate-dose animals, glycerol reduced the incidence of benign and malignant tumors and that of multiple tumors. The high dose of glycerol reduced the incidence of hyperplasia in animals not developing skin tumors. In effect, glycerol appears to modify the incidence of malignant tumors, benign tumors, hyperplasia, and unaffected skin. This suggests a sequential relationship between epithelial hyperplasia, benign tumors, and malignant tumors of the skin in response to topical carcinogens, with glycerol impeding the conversion of hyperplasia to neoplasia and the transition of benign to malignant tumors and, at high dose, inhibiting skin hyperplasia. (9 refs)

78-5048 **Mutagen-Carcinogens in Food, with Special Reference to Highly Mutagenic Pyrolytic Products in Broiled Foods.** (Eng) Sugimura, T. (Natl. Cancer Center Res. Inst., Tsukiji 5-1-1, Chuoku, Tokyo, Japan); Nagao, M.; Kawachi, T.; Honda, M.; Matsumoto, H.; Yahagi, T.; Seino, Y.; Sato, S.; Matsukura, N.; Matsushima, T.; Shirai, A.; Sawamura, M. *In: Human Risk Assessment. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book C), 583 pp.; 1561-1577; 1977.

The mutagenic activity (MA) of a large number of chemicals and of common food components was tested by a modified *Salmonella typhimurium*/liver microsome assay. Of 400 chemicals tested, 140 were reported to be carinogenic, and 121/140 (87%) were mutagenic to *Salmonella.* Smoke condensate from broiled fish was mutagenic to *Salmonella* with or without metabolic activation. Dimethyl sulfoxide (DMSO) extracts of the charred surface of broiled fish and beef steak were mutagenic to *Salmonella* with metabolic activation. Smoke condensate from broiled steak showed very low mutagenicity. When MA was expressed in terms of benzo(a)-pyrene (BP) equivalents, the smoke condensate from broiled fish was calculated to contain 10,000 times the MA of its BP content (9 nanograms BP in smoke condensate from 100 g fish). Smoke produced by heating protein of high L-tryptophan content and L-tryptophan itself possessed strong MA. Smoke from heating carbohydrate and vegetable oil was not mutagenic. The MA of low-, medium, and high-tar cigarettes was assayed and expressed in BP equivalents. The BP equivalents/mg tar were similar, indicating that the equivalents are a direct function of the amount of tar. Of 35 mycotoxins tested, 10 were shown to be mutagenic for the first time. Since these compounds are likely to be food contaminants, their carcinogenicity in animals should be examined fully. (40 refs)

78-5049 **Ingested Mutagens from Opium and Tobacco Pyrolysis Products and Cancer of the Oesophagus.** (Eng) Hewer, T. (Univ. Bristol, Bristol, England); Rose, E.; Ghadirian, P.; Castegnaro, M.; Bartsch, H.; Malaveille, C.; Day, N. *Lancet* 2(8088): 494-496; 1978.

The mutagenicities of crude opium, opium dross (the residue from the opium pipe), shireh (refined opium extract), injonga (the tobacco residue extracted from the pipe stem), and isixaxa (the tobacco residues in the pipe) were determined by plate incorporation assays with *Salmonella typhimurium* strains TA98 and TA100. These substances are commonly sucked or chewed in northeast Iran and the Transkei, South Africa, where the incidence of esophageal cancer is high. The opium dross was mutagenic in both tester strains in the presence of rat liver microsomes, whereas the crude opium and shireh were not. Therefore, it is likely that mutagenic pyrolysis products are formed during opium smoking. Both injonga and isixaxa showed a concentration-dependent increase in mutagenicity in the presence of rat liver microsomes. The data indicate that opium and tobacco pyrolysis products

uld be involved in the etiology of esophageal cancer in the anskei and northeast Iran. (14 refs.)

-5050 **Effects of LSD on Human Chromosomes.** (Eng) Muneer, R. S. (Dept. Biochemistry and Molecu- Biology, Univ. Oklahoma Health Sciences Center, Okla- ma City, OK, 73190). *Mutat Res* 51(3): 403-410; 1978.

e effects of lysergic acid diethylamide-25 (LSD-25) and D tartrate (1.0 or 10 μg/ml) on human chromosomes were died using phytohemagglutinin-stimulated heparinized od lymphocytes from six normal individuals. Control lym- ocyte cultures were left untreated or were treated with tomycin C (0.1 μg/ml). There was no significant difference chromosome aberrations between control cells and those osed to either concentration of LSD-25 or LSD tartrate 24 hr or either concentration of LSD-25 for 72 hr. Howev- the aberration frequency was significantly higher in cells ated with LSD tartrate for 72 hr compared with controls. st of the aberrations represented the results of single break nts, and complex aberrations such as dicentrics and quad- adials were not seen. Exposure to mitomycin C induced gnificantly elevated incidence of severe chromosome aber- ions. LSD-25 at 10 μg/ml had no significant effect on the wth rate, viability, mutation, or recombination frequency *Escherichia coli*; the growth rate or rate of macromolecular thesis in mouse L cells; or the growth of human fibrob- s. LSD-25 at 100 μg/ml had a toxic effect on mouse and nan cells. The data permit no conclusions concerning pos- e deleterious effects of LSD-25 at reasonable doses on hu- n somatic cells. (16 refs.)

-5051 **Gas-Liquid Chromatographic Determination of Nitrate and Nitrite in Cheese, Ham, Fish Sau- e, Cod Roes, and Salmon Roes.** (Eng) Toyoda, M. (Hoen- a, Higashi-ku, Natl. Inst. Hygienic Sciences, Osaka nch, Hoenzaka, Higashi-ku, Osaka 540, Japan); Suzuki, Ito, Y.; Iwaida, M. *J Assoc Off Anal Chem* 61(3): 508-512; 8.

gas-liquid chromatographic method based on extraction the reaction product of nitrate and 2,4-xylenol has been eloped for determining nitrates and nitrites in foods. After tillation, the nitrite residue is oxidized to nitrate with assium permanganate and then chromatographed in the ne manner as nitrate. Recoveries from several foods were %-100% for nitrate and 80%-100% for nitrite; the limit sensitivity was 0.1 ppm for both. (8 refs)

5052 **Nitrite and Nitrate Are Formed by Endogenous Synthesis in the Human Intestine.** (Eng) Tan- baum, S. R. (Dept. Nutrition and Food Science, Massa- setts Inst. Technology, Cambridge, MA, 02139); Fett, D.; Young, V. R.; Land, P. D.; Bruce, W. R. *Science* 200(4349): 1487-1489; 1978.

Nitrate balance studies were performed in healthy Caucasian men to assess the extent of nitrate intake in the general population. Six 68- to 72-yr-old men were given a diet of their own choosing for 1 wk, a protein-free diet for 10 days, and a diet containing 0.8 g/kg egg protein for 10 days. Large day-to-day fluctuations in urinary nitrate were noted with both the protein-free and 0.8-g protein diets; there was no tendency to equilibrium. For each subject, the excretion of nitrate greatly exceeded the dietary intake of nitrate. In a second study, eight 25- to 40-yr-old men submitted single fecal samples for analysis, and six 25- to 30-yr-old men submitted samples of ileostomy effluent. Great variations were found among individuals, but all 14 samples contained nitrite. Five of the fecal samples also contained nitrate. In a series of fecal samples from two individuals, nitrite was always present and nitrate was sometimes present. Substances in the diet that react with nitrite (eg, ascorbic acid) did not appear to have a significant effect on nitrite concentration at pH > 5.5. It is suggested that heterotrophic nitrification of ammonia or organic nitrogen compounds takes place in the upper, aerobic portion of the intestine. As material passes through the intestine, the environment becomes more anaerobic, leading to the accumulation of nitrate as well as nitrite. Thus, human exposure to nitrite is much greater than previously recognized. Absorbed nitrite is rapidly destroyed in the blood, but nitrate is recycled into the saliva, stomach, and bladder; in this way, intestinal nitrification may contribute to the etiology of human cancer. (21 refs)

78-5053 **Reversible Interconversion of N-Nitroso(2-methylamino)acetonitrile and 3-Methyl -5-amino- 1,2,3- oxadiazolium Chloride and Related Reactions.** (Eng) Vohra, S. K. (Dept. Chemistry, Temple Univ., Philadelphia, PA, 19122); Harrington, G. W.; Swern, D. *J Org Chem* 43(9): 1671-1673; 1978.

As part of an ongoing study of the anchimeric effects of the N-nitroso group in conjunction with studies of structure-biological activity relationships in N-nitrosamines, N-nitroso(2-methylamino)acetonitrile (I) and N-nitroso(3-methylamino)propionitrile (II) were reacted with anhydrous HCl in nonaqueous solvents. Compound I quickly yielded 3-methyl-5-amino-1,2,3-oxadiazolium chloride III, virtually quantitatively, suggesting anchimeric assistance by the nitroso group. Treatment with aqueous base converted III back to I. Compound II did not yield a cyclic product. (8 refs)

78-5054 **Chromosomal Proteins in Hepatocarcinogenesis.** (Eng) Tsanev, R. (Inst. Biochemistry, Bulgarian Acad. Sciences, Sofia, Bulgaria); Hadjiolov, D. *Z Krebsforsch* 91(3): 237-247; 1978.

Sodium dodecyl sulfate-polyacrylamide gel electrophoresis was used to study the chromosomal proteins of rat liver during nitrosomorpholine (NM)-induced hepatocarcinogenesis and in the resulting primary hepatomas and metastases. Male Wistar rats were fed NM in the drinking water (10 mg/kg, 6 days/wk, for 5 mo). Experimental and control rats were killed 30, 90 and 220 days after the start of the experiment. Chromatin was isolated from liver nuclei in the absence and presence of phenylmethylsulfonylfluoride (PMSF), a powerful inhibitor of serine proteases. Trabecular- and vesicular-type hepatocellular carcinomas plus two cases of metastases to the omentum lymph nodes were observed. During carcinogenesis, the pattern of nonhistone chromosomal proteins (NHCP) from liver chromatin isolated in the absence of PMSF was altered strikingly. Many high-mol-wt NHCP disappeared. In the presence of PMSF, however, no qualitative alterations could be detected. Thus, the liver homogenates of NM-treated animals exhibited an increased proteolytic activity. Contractile protein and histone fractions were selectively preserved. Only slight quantitative changes were noted in the hepatomas: an increase in the 43,000 (43K)- and 63K-dalton protein bands and a decrease in the fast-moving histone subfraction H1°. Apparently, primary hepatomas have an overall NHCP pattern similar to that of normal liver. Quantitative and qualitative differences were found in the metastases: a significant decrease in protein bands corresponding to the contractile proteins α- and β-tubulin and actin, a significant increase in the 63K-dalton protein, the appearance of new proteins of approx 60K, 90K, and 120K daltons, and the complete disappearance of H1°. It is suggested that the hepatoma cells that migrate to form metastases have undergone further malignant progression associated with changes in their chromosomal proteins. (53 refs)

78-5055 **The Effect of Estradiol-17-phenylpropionate and Estradiol Benzoate on N-Nitrosomorpholine-induced Liver Carcinogenesis in Ovariectomized Female Rats.** (Eng) Taper, H. S. (Dept. General Pathology and Neuropathology, Univ. Louvain, Av. Mounier 52, ANPG 52.60, B-1200 Brussels, Belgium). *Cancer* 42(2): 462-467; 1978.

The effects of synthetic estrogens on N-nitrosomorpholine (NNM)-induced liver carcinogenesis in ovariectomized Wistar R rats were determined. Approx 1 mo after ovariectomy, the animals were divided into four groups. Group 1 received NNM (2.6 mg/100 g, 5x/wk for 3 wk, in aqueous soln, by intragastric intubation). Group 2 received NNM plus a single dose of 645 μg/100 g Dimenformon Prolongatum (500 μg estradiol-17-phenylpropionate and 145 μg estradiolbenzoate/100 g) at the beginning of carcinogen treatment. Group 3 received NNM and, after a 2-wk interval, Dimenformon Prolongatum at 3-wk intervals until the end of the experiment. Group 4 received estrogen treatment only, as in Group 3. Animals were sacrificed approx 300 days after the beginning of NNM treatment. Twenty-nine animals were lost as a result of ovariectomy complications and NNM toxicity and they were excluded from the calculations. Liver foci, nodule or tumors were noted in 25/31 Group 1, 19/21 Group 29/31 Group 3, and 0/27 Group 4 animals. Hepatocellul tumors with varying degrees of differentiation were noted 3 Group 1, 2 Group 2, and 9 Group 3 rats. Enlarged hyp physes were found in all animals in Groups 3 and 4 in whic autopsy of the skull was performed; no such enlargemen were noted in the other groups. Since no Group 4 anima developed foci, nodules, or hepatocellular carcinomas, it suggested that the estrogens were acting as tumor promoto and not as initiators of liver carcinogenesis. (24 refs.)

78-5056 **Nitrosomorpholine-induced Tumors in Fis** (Bul) Khudolei, V. V. (N. N. Petrov Res. Ins Oncology, Leningrad, USSR); Balanski, R. M. *Onkologi* 14(4): 168-173; 1977.

The carcinogenic effect of nitrosomorpholine (NM) was stu ied in guppies (*Lebistes reticulatus*) and *Brachydan rerio*. Twenty specimens of *Br. rerio* were exposed NM for 28 wk; the NM concentration in the water w gradually increased from 100 to 320 ppm. Thirte animals were alive at the time the first tumor w detected. Seven tumors were found in four anima and the av latent time was 16 wk. The tumors includ 4 hepatocellular carcinomas, 2 intestinal adenocarcin mas, and 1 mesenchymoma of the abdominal cavi Thirty guppies were exposed to NM for 23 wk; the co centration was increased from 75 to 250 ppm. Nine a mals were alive at the time the first tumor was detected. Eig tumors (4 hepatocellular carcinomas, 3 hepatic ade mas, and 1 cystocholangiolar cyst) were found in eig animals. The av latent period was 30 wk. Forty spe mens of *Br. rerio* were exposed to 300 ppm NM for wk; 11 were alive at the time the first tumor was tected. Five tumors (2 intestinal adenocarcinom and 3 hepatocellular carcinomas) were found in fo animals. The av latent period was 22 wk. No tum were found in 90 controls of both species. The findin indicate the potent carcinogenic effect of NM in fi (15 refs)

78-5057 **Detection and Determination of N-Nitrosamin Acids by Thin-Layer Chromatography Usin Fluorescamine.** (Eng) Young, J. C. (Chemistry and Biolog Res. Inst., Agriculture Canada, Ottawa, Ontario K1A 0C Canada). *J Chromatogr* 151(2): 215-221; 1978.

A procedure for the detection and determination of N-n trosoamino acids on activated silica gel thin-layer chromato graphic plates is described. Using this technique, N-n trososarcosine, N-nitrosoproline, and N-nitroso-4-h droxyproline could be detected as fluorophors at the to 30-nanogram level. An application of this method the detection of these acid compounds in uncook bacon is described. (58 refs)

8-5058 Occurrence and Determination of N-Nitroso-3-hydroxypyrrolidine in Cured Meat Products. Eng) Janzowski, C. (Inst. Toxicology and Chemotherapy, German Cancer Res. Center, Im Neuenheimer Feld 280, D-900 Heidelberg, W. Germany); Eisenbrand, G.; Preussmann, R. *J Chromatogr* 150(1): 216-220; 1978.

An analytical method for the isolation and determination of N-nitroso-3-hydroxypyrrolidine, a mutagen in the *Salmonella typhimurium* assay, in foods is presented. The amount of this compound in bacon, boiled ham, and bologna sausage was found to be 1-7 ppb. (8 refs)

78-5059 Crypt Hyperplasia Occuring During Dimethylhydrazine Carcinogenesis in the Jejunal Mucosae of Rats (Meeting Abstract). (Eng) Sunter, J. P. (Dept. Pathology, Univ. Newcastle-upon-Tyne, Newcastle-upon-Tyne, England); Appleton, D. R.; Watson, A. J.; Wright, N. A. *J Anat* 126(2): 437; 1978. (no refs)

78-5060 Glycoprotein Metabolism in Normal Proximal and Distal Rat Colon and Changes Associated with 1,2-Dimethylhydrazine-induced Colonic Neoplasia. (Eng) Freeman, H. J. (Gastrointestinal Res. Lab., Veterans Admin. Hosp., 4150 Clement St., San Francisco, CA, 94121); Kim, Y.; Kim, Y. S. *Cancer Res* 38(10): 3385-3390; 1978.

The mucosal sugar content as well as the activities of several glycosyltransferases and some glycosidases were determined in the proximal and distal colon of normal male Wistar rats and in rats undergoing 1,2-dimethylhydrazine (DMH)-induced carcinogenesis. In normal rats, differences in total hexose content as well as the activities of several glycosyltransferases and some glycosidases were noted. This indicated that glycoprotein content and metabolism are different at these two sites. In rats receiving DMH (weekly injections of 25 mg/kg from age 6 to 24 wk, sacrifice at 52 wk), significant alterations in hexose content and two galactosyltransferase activities were observed in uninvolved mucosa following DMH administration. Furthermore, significant reductions in sugar content, three of four glycosyltransferase activities, and two hexosaminidase activities were observed in colonic tumors. These data indicate that significant alterations in glycoproteins occur in association with chemical carcinogenesis in both colonic tumors and uninvolved rat colonic mucosa. Furthermore, these studies emphasize the importance of considering the regional differences in quantity and quality of glycoproteins in normal colonic mucosa when studying pathological states. (37 refs.)

78-5061 Effects of Diet on Colon Carcinogenesis and the Immune System in Rats Treated with 1,2-Dimethylhydrazine. (Eng) Bansal, B. R. (Dept. Surgery, Alma Dea Morani Lab. Surgical Immunobiology, Medical Coll. Pennsylvania, Philadelphia, PA, 19129); Rhoads, J. E.; Bansal, S. C. *Cancer Res* 38(10): 3293-3303; 1978.

The effects of different diets on colon carcinogenesis by 1,2-dimethylhydrazine (DMH) and on the immune system were determined in male W-Fu rats. Six different diets were used: standard diet (1), semisynthetic diet (2), high-carbohydrate diet (3), high-fat diet (4), high-carbohydrate diet with lard (5), and high-fat diet with lard (6). In the first experiment, diets 1-4 were initiated upon weaning and DMH (15 mg/kg weekly in two divided doses, sc) was administered for 190 days beginning when the rats were 35 days old. In the second experiment, diets 1, 5, and 6 were initiated upon weaning and DMH was given for 133 days beginning at 45 days of age. The rats were followed by sequential laparotomies until death for the development of gastrointestinal (GI) tumors. Tumors appeared earlier and the total number of GI tumors, particularly those of the colon, was higher in rats fed diets 5 and 6. These GI tumors metastasized more frequently and the survival of the rats, after the appearance of the first GI tumor, was significantly shortened. Diet 3 reduced the number of GI tumors and delayed their appearance. Diet 2 accelerated the appearance of colon tumors without increasing the total number of GI tumors over the life-span of the animals. Serum cholesterol levels evaluated during carcinogenesis suggested a correlation between these levels and the increased frequency of colon tumors. The alterations in serum IgG levels, lymphocyte counts, and surface immunoglobulin-bearing lymphocytes, evaluated at different times during carcinogenesis, suggested a biphasic (M-type) immune response. Serum IgG levels were significantly depressed in rats fed diets 2, 4, 5, and 6 compared with levels in rats fed diet 1. However, the pattern of the immune response was similar in the groups of rats fed different types of diets. (39 refs.)

78-5062 Influence of Surgical Anastomosis on DMH Carcinogenesis in the Rat Bowel (Meeting Abstract). (Eng) Teague, C. A. (Dept. Pathology, Univ. Auckland, Auckland, New Zealand); Gavin, J. B.; Whitehouse, S. *NZ Med J* 86(595): 246; 1977. (no refs)

78-5063 Carcinogenicity of 1,2-Dimethylhydrazine Dihydrochloride (DMH) in BALB/c Mice: Influence of the Route and Dose of Administration (Meeting Abstract). (Eng) Izumi, K. (Second Dept. Pathology, Sch. Medicine, Tokushima Univ., Tokushima, 770, Japan); Furuya, K.; Otsuka, H. *In: Summary Program and Abstracts of Papers. Proceedings of the 3rd Asian Cancer Conference Held by the Philippine Cancer Society under the Auspices of the Asian Federation of Organizations for Cancer Research and Control in Manila, 26-30 September, 1977.* Philippine

Cancer Society. (Manila, Philippines): 184 pp.; 110-111; 1977. (no refs)

78-5064 **Inhibition of DNA Synthesis by 1,2-Dimethylhydrazine and Methylazoxymethanol Acetate in Rabbit Colon Mucosa in Organ Culture.** (Eng) Mak, K. M. (Dept. Anatomy, Mount Sinai Sch. Medicine, New York, NY, 10029); Chang, W. W. *J Natl Cancer Inst* 61(3): 799-805; 1978.

Colon mucosa explants from New Zealand White rabbits were cultured and used to study the effect of 1,2-dimethylhydrazine (DMH) and methylazoxymethanol acetate (MAM acetate) on DNA synthesis in the epithelial cells. When maintained in organ culture, the mucosa showed near-normal morphology and a linear incorporation of ^{3}H-thymidine into mucosal DNA up to 36 hr of incubation. Explants from the descending colon had a higher DNA synthetic activity than did other segments of the large bowel. Inhibition of DNA synthesis in the explants by DMH and MAM acetate was dose-dependent. After 18 hr of incubation, MAM acetate inhibited DNA synthesis at concentrations of 50, 100, 150, and 200 μg/ml. Little or no inhibition was observed with the same concentrations of DMH. At a concentration of 200 μg/ml and after only 3 or 6 hr of incubation, however, both carcinogens significantly inhibited DNA synthesis. With a longer incubation time, the inhibitory effect of DMH appeared to be reversible, but DNA synthesis was continuously inhibited by MAM acetate up to 18 hr of incubation. Neither DMH nor MAM acetate altered the uptake of ^{3}H-thymidine during 18 hr of incubation. No morphologic changes were seen in explants treated with 200 μg/ml MAM acetate for 18 hr. Physostigmine sulfate, a cholinesterase inhibitor, had no effect on the MAM acetate-induced inhibition of DNA synthesis. These findings indicate that DMH and MAM acetate have a direct effect on the colon mucosa, and they suggest that colon epithelial cells contain enzymes capable of activating DMH and MAM acetate to their alkylating carcinogens. (33 refs.)

78-5065 **Carcinogenic Action of N-Nitroso Compounds. 7. Methyl-, Trideuteromethyl-, Ethyl-, n-Propyl-, n-Butyl-, and Acetoxymethylnitrosamine and Methylbutyroxymethylnitrosamine.** (Ger) Wiessler, M. (Institut fur Toxikologie und Chemotherapie, Deutschen Krebsforschungszentrum, Im Neuenheimer Feld 280, D-6900 Heidelberg, W. Germany); Habs, M.; Schmahl, D. *Z Krebsforsch* 91(3): 317-322; 1978.

Methyl-, trideuteromethyl-, ethyl-, n-propyl-, n-butyl-, and acetoxymethylnitrosamine and methylbutoxymethylnitrosamine were examined for carcinogenicity in SD rats. All compounds were carcinogenic, inducing forestomach tumors with approx the same latent period. The total doses necessary for tumor induction were related to the length of the alky chain and, hence, to water solubility. (18 refs.)

78-5066 **Synthesis of ^{14}C-Labelled Nitrosamines. IV Synthesis of ^{14}C-Methyl(1-acetoxy)methyl Nitrosamine and 1-^{14}C-Ethyl(acetoxy)ethyl Nitrosamine.** (Eng) Braun, H. (Inst. Toxicology and Chemotherapy, Germa Cancer Res. Center, Im Neuenheimer Feld 280, 6900 Heidelberg, W. Germany); Wiessler, M. *J Labelled Compd Radiopharm* 14(6): 887-892; 1978.

Experimental procedures for the synthesis of ^{14}C-methyl(1-acetoxy)ethylnitrosamine and 1-^{14}C-ethyl(1-acetoxy) ethylnitrosamine are presented. The respective yields of th two compounds were 16.3% and 33.3%. (6 refs.)

78-5067 **Possible Neuropharmacological Regulation o Diethylnitrosamine-induced Chemical Carcinogenesis.** (Rus) Gurkalo, V. K. (Lab. Chemical Carcinogen N. N. Petrov Res. Inst. Oncology, Leningrad, USSR); Zabe hinskii, M. A. *Farmakol Toksikol* 41(3): 338-342; 1978.

The effect of neurophilic agents on diethylnitrosamin (DENA)-induced carcinogenesis was evaluated in fou groups of random-bred rats who received DENA with drink ing water (100 mg/liter) plus (Group 1) sc injections of atro pine (12 mg/kg, 3x/wk), (Group 2) sc injections of proserin (50 μg/kg 3x/wk), (Group 3) sc injections of an adrenergi alpha blocking agent (a 3-phenylpyrrolidine derivative: 2 mg/kg , 3x/wk), or (Group 4) no further treatment. The rat were sacrificed at 6 mo, and the activity of monoamine oxi dase (MAO) in liver mitochondria was assessed. The inci dence of hepatic and esophageal tumors was increased signifi cantly in Group 1, being 12/15 and 7/15, respectively compared with 7/15 and 3/15 Group 4. The adrenergic alph blocking agent did not affect the incidence of hepatic an esophageal tumors (6/15 and 2/15), but proserine decrease both the incidence (2/15 and 1/15) and multiplicity of tumo nodes. All three agents significantly increased MAO activit (from 2.0 IU in Group 4 to 3.20 in Group 1, 3.4 in Grou 2, and 2.65 in Group 3). (13 refs)

78-5068 **Ultrastructure of N-Diethylnitrosamine In duced Tumours in the Nasal Olfactory Regio of the Syrian Golden Hamster.** (Eng) Reznik-Schuller, H (Frederick Cancer Res. Center, P.O. Box B, Frederick, MD 21501). *J Pathol* 124(3): 161-164; 1978.

Tumors of the nasal olfactory region induced in five Syria golden hamsters after sc treatment with N-diethylnitrosa mine (DEN: 17.8 mg/kg 1x/wk for 20 wk) were examine electron microscopically. The neoplasms consisted of two cel

types, one of which contained membrane-bound, dense-cored, neurosecretory-type granules. These dense-cored granules were frequently found closely associated with the Golgi apparatus, and a few were identified in cells undergoing mitosis. The other cell type, characterized by its content of abundant ribosomes and polyribosomes, occasionally also exhibited mitosis. The findings demonstrate that the DEN-induced neoplasms originated from the poorly differentiated precursors of olfactory sensory cells (neuroblasts) and from precursors of Sertoli cells (basal cells). (10 refs)

78-5069 **Nucleic Acids from Subcellular Fractions of N-Nitrosodiethylamine-induced Hepatoma in Mice. II. Changes in Gene Expression During Tumor Progression.** (Eng) Shaposhnikov, J. D. (Petrov Res. Inst. Oncology, USSR Ministry Public Health, Leningrad 188646, USSR); Ratovitski, E. A. *Neoplasma* 25(2): 145-152; 1978.

The hybridization properties of in vivo-labeled nuclear and mitochondrial RNA's of an N-nitrosodiethylamine-induced transplantable hepatoma were investigated in C3HA mice at early (5 and 6) and late (60) passages. During tumor progression, the repression of the nuclear genome noted at early stages was replaced by derepression at later stages. As a result, the percentage of nuclear RNA that hybridized with nuclear DNA increased, and new classes of hybridizable sequences appeared. These results are related only to the repetitive nucleotide sequences. The hybridizability of mitochondrial RNA with nuclear DNA was not changed. (26 refs)

78-5070 **The Determination of N-Nitrosodiethanolamine in Cutting Fluids.** (Eng) Williams, D. T. (Environmental Health Directorate, Health Protection Branch, Tunney's Pasture, Ottawa, Ontario K1A 0L2, Canada); Benoit, F.; Muzika, K. *Bull Environ Contam Toxicol* 20(2): 206-211; 1978.

Twenty-four samples of cutting fluid concentrates were analyzed by thin layer chromatography for the presence of N-nitrosodiethanolamine (NDETA). Nine of these samples contained nitrite at levels up to 9.8%; NDETA (0.4-4.2 mg/g) was only found in the nitrite-containing samples. (8 refs.)

78-5071 **DNA Phosphotriesters as Indicators of Cumulative Carcinogen-induced Damage.** (Eng) Shooter, K. V. (Div. Carcinogenesis, Inst. Cancer Res., Pollards Wood Res. Station, Nightingales Lane, Chalfont St., Giles, Bucks, England). *Nature* 274(5671): 612-614; 1978.

Female Chester Beatty hooded rats were fed dimethylnitrosamine (DMN) or diethylnitrosamine (DEN) in the drinking water (0.1-5 ppm, mean rate of consumption, 2-75 μg/rat/-day) continuously for 6-54 wk or they were inoculated ip with single doses of 2-20 mg/kg DMN, and the distribution of phosphotriesters (PTE) in the DNA of lung, liver, and kidney was compared. The concentration of PTE was determined by the differential alkaline hydrolysis method. In the long-term feeding experiment, all doses of DMN induced significant amounts of methyl PTE in the liver DNA. At the highest dose, significant and increasing amounts of PTE were observed in the lung DNA; however, at lower doses, the data on lung DNA were inconclusive. In kidney DNA, significant positive results were observed in only 3/18 experiments, which agrees with observations that long-term feeding of this compound does not tend to induce kidney tumors. After continuous ingestion of DEN, significant concentrations of ethyl PTE were found in the DNA of liver, kidney, and lung, even at low dose rates. After 1 yr, significant amounts of specific lesions could be detected in tissue DNA, even in rats receiving only 2 μg/day of either carcinogen. With a single dose of DMN, most of the methyl PTE were detected in the liver, but an appreciable fraction of DMN was metabolized in the kidney and lung. Since this assay for PTE involves simply the determination of the number of chain breaks produced in DNA by alkaline hydrolysis, it should have a fairly general applicability, the nature of the chemical moiety reacting with the phosphate group being, in general, not important. (13 refs.)

78-5072 **Hepatic RNA Resistance to Enzymatic Degradation During Hepatocarcinogenesis in Rats.** (Rus) Voronova, L. A. (N. N. Petrov Res. Inst. Oncology, USSR Ministry Health, Leningrad, USSR); Ivanov, S. D. *Vopr Onkol* 24(5): 30-35; 1978.

The resistance of hepatic RNA to degradation by serum RNase was investigated during heptocarcinogenesis induced in rats by a 6-mo feeding of diethylnitrosamine (DENA). Resistance to RNase degradation was used as a criterion of changes in the spatial configuration of the polynucleotides. In the precancerous state and within the pH range studied (5.1, 7.6, and 8.5), the resistance of total, cytoplasmic, ribosomal, and transfer RNA to enzymatic degradation increased considerably and then fell. With tumor development, RNA resistance to enzymatic cleavage increased again and, in most cases, exceeded control levels. A comparison of these findings with those obtained after treatment of rats with CCl_4 indicated that the carcinogenic effect of DENA on rat liver is accompanied by changes in the spatial configuration of cytoplasmic RNA molecules. (16 refs)

78-5073 **Studies on the Gastrointestinal Absorption of N-Nitrosamines: Effect of Dietary Constituents.** (Eng) Agrelo, C. (British Industrial Biological Res. As-

soc., Woodmansterne Road, Carshalton Beeches, Surrey SM4 4DS, England); Lake, B. G.; Phillips, J. C.; Gangolli, S. D.; Longland, R. C. *Toxicology* 10(2): 159-167; 1978.

The effects of fat, protein, and carbohydrate on the rates of disappearance of ^{14}C-labeled N-nitrosodimethylamine (DMN) and other nitrosamines from the small intestine of male Sprague-Dawley rats were investigated. Following overnight starvation, the rats were given, by po intubation, ^{14}C-DMN (5 mg/kg) dissolved in isotonic saline soln, corn oil, or casein soln (5% wt/volume). Intestinal absorption studies showed that the presence of fat markedly reduced the rate of disappearance of DMN at concentrations of 4-200 μg/ml. Protein and carbohydrate had little effect on absorption rate. Investigations of the absorption of N-nitrosodiethylamine, N-nitropyrrolidine, and N-nitrosopiperidine from isotonic saline and lipid emulsion showed that lipids also retarded the disappearance of these compounds from the small intestine. In vitro absorption studies, using everted intestinal sac preparations, showed that the small intestinal tract of the rat can degrade DMN. Factors that prolong the retention time of nitrosamines in the gut should facilitate the degradation of these compounds by the metabolic activity of intestinal cells and, possibly, by gut flora and thereby reduce the effective concentration of nitrosamine reaching target organs of the body. (19 refs.)

78-5074 **Experimentally Induced Hemangioendotheliomas in the Liver of Mastomys Using Dimethylnitrosamine (Meeting Abstract).** (Ger) Wayss, K. (Heidelberg, W. Germany); Bannasch, P.; Mattern, J.; Volm, M. *Zentralbl Allg Pathol* 122(3): 289; 1978. (no refs)

78-5075 **Stimulation of Microsomal Dimethylnitrosamine-N-demethylase by Pretreatment of Mice with Acetone.** (Eng) Sipes, I. G. (Dept. Anesthesiology, Univ. Arizona, Tucson, AZ, 85724); Slocumb, M. L.; Holtzman, G. *Chem Biol Interact* 21(2/3): 155-166; 1978.

Male C57BL/6J mice were pretreated with acetone (Ac, 15-60 millimoles/kg in normal saline, ip) or Aroclor 1254 (Ar, 500 mg/kg in sesame oil, ip); and the relationship between in vivo microsomal enzyme modifiers and in vitro dimethylnitrosamine (DMN) metabolism was investigated. Ac and Ar are known to influence DMN-N-demethylase activity. Microsomes were isolated from the livers of mice sacrificed 2-48 hr after Ac injection, 4 days after Ar injection. They were then incubated with 0.1-200 mM DMN. Ac enhanced the in vitro microsomal activity of DMN-N-demethylase, as measured by formaldehyde production from DMN. The enhancement was dose- and time-dependent, with max activity occurring 16 hr after Ac injection. There was a concomitant increase in the covalent binding of ^{14}C-DMN to RNA, protein, and DNA. Four distinct Km values that were dependent on DMN concentration were noted for the N-demethylase in microsomes from control mice. Only one Km value was observed for the N-demethylase in microsomes from Ac-treated animals, but it was significantly lower (0.09 mM) than the lowest control value (0.2 mM). Compared with control microsomes, Ac significantly increased DMN-N-demethylation at 1 and 10 mM DMN, but not at 100 mM. DMN-N-demethylase activity in microsomes from Ar-treated mice was significantly decreased at 1 mM DMN and significantly enhanced at 100 mM. It is suggested that there may be multiple forms of DMN-N-demethylase that are dependent on DMN concentration and that respond differently to modifiers of the microsomal drug-metabolizing enzymes. (31 refs.)

78-5076 **Nitrosamine Formation in Bladder Infections and Its Role in the Etiology of Bladder Cancer.** (Eng) Radomski, J. L. (Dept. Pharmacology, Univ. Miami Sch. Medicine, Miami, FL); Greenwald, D.; Hearn, W. L.; Block, N. L.; Woods, F. M. *J Urol* 120(1): 48-50; 1978.

To evaluate the role of nitrosamine formation in the etiology of bladder cancer, dimethylnitrosamine (DMN) formation was determined in urine specimens incubated in vitro with sodium nitrite and aminopyrine or tetracycline and in urine specimens from untreated and tetracycline-treated patients with urinary tract infections. DMN was formed during the incubation of aminopyrine and, to a lesser extent, tetracycline in urine containing sodium nitrite. Small but significant amounts of DMN were also formed in control urine specimens. DMN was formed during incubations of nitrite-containing urine with diphenyhydramine, but not with dimethylaminoethanol, sulfisoxazole, or chloroquine. DMN was found in the urine of 3/10 patients with urinary tract infections before therapy, the concentration being correlated with the presence of nitrite in the urine. The highest concentrations of nitrite and DMN were produced by *Proteus mirabilis*. Therapy with tetracycline rapidly decreased the concentrations of DMN, thus exonerating the drug from any involvement in the induction of bladder cancer by this mechanism. (11 refs.)

78-5077 **Kinetic Studies on the Formation of Nitrosamines. I. Formation of Dimethylnitrosamine in Aqueous Solution of Perchloric Acid.** (Eng) Cachaza, J. M. (Departamento de Quimica Fisica, Instituto de Investigaciones Quimicas, C.S.I.C, Universidad de Santiago, E-Santiago de Compostela, Spain); Casado, J.; Castro, A.; Lopez Quintela, M. A. *Z Krebsforsch* 91(3): 279-290; 1978.

The kinetics of nitrosation of dimethylamine (DMA) in aqueous perchloric acid soln were determined by differential spectrophotometry. Absorbance was measured at 323 nanometers, and the reaction was performed at a temperature of 310 K. The rate of the reaction was independent of amine concen-

ration over the range tested (0.25-2.0 M). The initial rate of itrosation was proportional to the square of the initial stoichiometric concentration of nitrite (3-7 x 10^2 M) in the overall ange of pH's studied (1.5-4.0). The degree of nitrosation by NO_2H_2+ (nitrosacidium ion) had practically no influence on he reaction rate. pH values were affected by the reaction nedia (ionic strength, neutral salts), and it was difficult to letermine their effect on the reaction rate. This rate was affected, however, by sodium perchlorate concentration. Nitroation was inhibited with increasing ionic strength (0.5-2.5 M) as a result of a decrease in the concentration of NO_2H lue to a change in pK-nitrite. The rate constant of the reaion was 4.8 ± 0.5 $10^{-5}M^{-2}s^{-1}$ (extrapolated to 298 K for comparison with previous rates obtained at that temperature). Nitrogen trioxide was the only nitrosating carrier that was ffective under the simplified conditions used. (30 refs)

78-5078 **Hormonal Regulation of Carcinogen Metabolism in Mouse Kidney.** (Eng) Bakshi, K. (Dept. Genetics, Litton Bionetics, Inc., Kensington, MD, 20795); Brusick, D.; Bullock, L.; Bardin, C. W. *In: Mechanisms of Carcinogenesis. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book B), 999 pp.; 683-695; 1977.

The effects of sex steroid hormones on the metabolism of dimethylnitrosamine (DMN) and N-2-fluorenylacetamide (AAF) by the mouse kidney were studied. Kidney microsomes from androgen-insensitive male (*tfm/y*) mice activated DMN to the same small extent as those from normal and carrier females and much less than those from normal males. In contrast, liver microsomes from all animals markedly activated DMN. Castration reduced kidney microsomal metabolism in males. Testosterone activated DMN in normal females and castrated males and enhanced carcinogen metabolism in normal males. Microsomes from untreated and testosterone-treated *tfm/y* mice produced no response; ie they had little ability to form mutagenic metabolites. Thus, androgens regulate DMN metabolism by modifying renal enzyme activity. The action of medroxyprogesterone acetate (MPA) on this microsomal enzyme system was also mediated via the androgen receptor. Kidney microsomes from normal female and *tfm/y* mice did not significantly activate AAF to a mutagen, whereas those from normal males were quite active. MPA increased the ability of kidney microsomes from female, but not *tfm/y*, mice to activate AAF. The data suggest that the sex-related differences in AAF-induced bladder tumors in mice are correlated with the differential metabolic activating capacities of male vs female kidneys. (27 refs.)

78-5079 **Diisopropanolnitrosamine-Induced Thyroid Tumors in Spraque-Dawley Rats (Meeting Abtract).** (Ger) Reznik, G. (Hannover, W. Germany). *Zentralbl Allg Pathol* 122(1/2): 146; 1978. (no refs)

78-5080 **Synthesis of Deuterium-labeled Nitrosomethylethylamines.** (Eng) Mangino, M. M. (Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21501); Lijinsky, W.; Singer, G. M. *J Labelled Compd Radiopharm* 14(5): 697-703; 1978.

Ethyl isocyanate, N-methylacetamide, N-methylacetamide-d_3, and N-methylacetamide-d_6 were reduced with lithium aluminum deuteride and then nitrosated with sodium nitrite to yield, respectively, nitrosomethyl(-d_3)ethylamine, nitrosomethylethyl(α-d_2)amine, nitrosomethylethyl(-d_5)amine, and nitrosomethyl(-d_3)ethyl(d_5)amine. All products were characterized by nuclear magnetic resonance spectrometry, UV spectrophotometry, and mass spectrometry. The mass spectra of nitrosomethylethylamine and the four deuterium labeled analogs showed patterns that confirmed previous conclusions about the fragmentation of the undeuterated compound. The chemical and isotopic purity of the products was deemed satisfactory for the biological testing of their relative carcinogenicity. (6 refs.)

78-5081 **Selective Induction of Pancreatic Ductular Tumors by Single Doses of N-Nitrosobis(2-oxopropyl)amine in Syrian Golden Hamsters.** (Eng) Pour, P. M. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NB, 68105); Salmasi, S. Z.; Runge, R. G. *Cancer Lett* 4(6): 317-323; 1978.

The effect of single injections of various N-nitrosobis(2-oxopropyl)amine (BOP) doses on the incidence of pancreatic neoplasms in Syrian golden hamsters was determined. Male and female animals received an sc injection of either 40 (Group 1), 20 (Group 2), 10 (Group 3), 5 (Group 4), or 2.5 mg/kg (Group 5); the animals were then observed for life and sacrificed when moribund. Pancreatic tumor incidence was dose-dependent, with Group 1 animals having the highest number of benign and malignant tumors and Group 5 animals having only a few benign neoplasms. Most of the tumors developed in the splenic lobe of the pancreas, which indicates that the carcinogen or its metabolites reach the pancreas systemically. Furthermore, most tumors were found along the main pancreatic ducts, suggesting that the neoplasms arise primarily from islet cell precursors, which are derivatives of ductular cells and germinative cells of the pancreas. Almost all tumors had ductular patterns, and they appeared to rise primarily from the intra- and periinsular ductules. A few tumors were also noted in the lungs, liver, gallbladder, and kidneys of some pancreatic tumor-bearing animals; animals without pancreatic tumors had no other tumors that could be related to treatment. The finding that pancreatic tumors were induced with 2.5 mg/kg BOP (2.5% of LD_{50}) demonstrates the high carcinogenic potency of this compound in the hamster pancreas. (15 refs.)

78-5082 **Synthesis of ^{14}C-Labelled Compounds. III. Synthesis of N-Nitroso-O,N-^{14}C-dimethylhydrox-**

ylamine. (Eng) Arjungi, K. N. (Cancer Res. Inst., Tata Memorial Center, Parel, Bombay 400026, India); Kruger, F. W.; Wiessler, M. *J Labelled Compd Radiopharm* 14(6): 913-918; 1978.

An experimental procedure for the synthesis of N-nitroso-O,N-^{14}C-dimethylhydroxylamine from ^{14}C-labeled dimethyl sulfate and N-hydroxyurethane is reported. The procedure resulted in a 49% yield of the nitrosamine. (9 refs.)

78-5083 **Distribution of 7-Methylguanine in Liver Chromatin DNA from Rats Treated with N,N-Di[^{14}C]Methylnitrosamine (Meeting Abstract).** (Eng) Galbraith, A. I. (Paterson Labs., Christie Hosp., Manchester, England); Itzhaki, R. F. *Br J Cancer* 38(1): 170-171; 1978. (1 ref)

78-5084 **Initiation of Chemical Carcinogenesis Requires Cell Proliferation.** (Eng) Cayama, E. (Dept. Pathology, Univ. Toronto, Medical Sciences Building, Toronto, Ontario M5S 1A8, Canada); Tsuda, H.; Sarma, D. S.; Farber, E. *Nature* 275(5675): 60-62; 1978.

A quantitative assay for the initiation of liver cancer was used to investigate whether cell replication exerts its first effect on initiation or on some later step in the carcinogenic process. The assay is based on the hypothesis that an early cell is resistant to the inhibitory effect of carcinogens on cell proliferation. It consists of measuring the number of foci of carcinogen-altered hepatocytes that are capable of responding to a stimulus for cell proliferation in the presence of a strong inhibitor of normal cell proliferation. Adult male Fischer 344 rats received a single ip dose of 60 mg/kg N-methyl-N-nitrosourea (MNU) followed 3 hr later by 67% partial hepatectomy (PH). Two weeks later, the rats received a diet containing 0.02% 2-acetylaminofluorene (2-AAF) and they were force-fed the mitogen α-hexachlorocyclohexane (HCH; 150 mg/kg) on days 7 and 9 after commencing 2-AAF. Foci of resistant phenotypically altered hepatocytes, positive for γ-glutamyltranspeptidase, were seen only in rats treated with MNU and PH. Very few foci were seen in rats receiving MNU + sham operation, vehicle alone + PH, or no treatment. Similar results were obtained with male Wistar rats. Furthermore, when CCl_4 (0.25 ml/100 g) replaced HCH as a stimulus for cell proliferation, significant numbers of γ-glutamyltranspeptidase-positive foci were again seen only in rats receiving MNU + PH. Recent results suggested that MNU is a much more efficient inducer of putative initiated cells when administered 18 hr after PH. Thus, initiation of carcinogenesis by MNU is intimately related to some change in the liver that occurs after two-thirds PH. Cell proliferation may stimulate the induction of putative preneoplastic hepatocytes by replication of carcinogen-damaged DNA before repair. (22 refs.)

78-5085 **Changes in Trace Element Levels During th Induction of Peripheral Nervous System T mors.** (Rus) Andronikashvili, E. L. (Inst. Physics, Tbili USSR); Sharashidze, L. K.; Mosulishvili, L. M.; Beniashvi D. S.; Kuchava, N. E.; Maisuradze, S. D. *Soobshch Ak Nauk Gruz SSR* 89(2): 473-476; 1978.

Changes in the amounts of various trace elements during th development and growth of induced peripheral nervous sy tem (PNS) tumors were evaluated in random-bred albi rats. The rats were subjected to weekly iv injections of m thylnitrosourea (MNU: 10 mg/kg). Every 30 days, some the animals were sacrificed, and the amounts of Fe, Zn, R Cr, Se, Co, Ba, Hg, Ag, and Sb were assessed in the bloo ischial nerve, and, after 3-5 mo, in the PNS tumors (benig reticular neurinomas). The levels of the elements did n change within the first 2 mo of the experiment. From day 9 however, amounts of Zn, Se, Cr, Fe, and Rb increase markedly. The rate of increase was max between days 60 an 120, ie, during the period when the tumors could not be y detected morphologically. (5 refs)

78-5086 **Chemical Carcinogenesis and Immunity: I munologic Status of Rats Treated with Meth nitrosourea.** (Eng) Zwilling, B. S. (Dept. Microbiology, Co Biological Sciences, Ohio State Univ., 484 W. 12th Av Columbus, OH, 43210); Filppi, J. A.; Chorpenning, F. W Koestner, A.; Rheins, M. S. *J Natl Cancer Inst* 61(3 731-735; 1978.

During the treatment of outbred Sprague-Dawley rats wi methylnitrosourea (MNU) or the noncarcinogenic analog d phenylnitrosamine, antibody levels to teichoic acid as well several parameters of lymphocyte and macrophage functi were assessed in animals not overtly stimulated with antige Groups of animals received 4.5, 1.5, or 0.5 mg/kg MNU gastric intubation every other week for 36 wk or similarl 4.5 mg/kg diphenylnitrosamine. MNU treatment did not a pear to alter most immunologic parameters studied. Son alterations occurred in natural antibody levels, in spleen w and in peripheral blood differentials of rats that had receiv the highest carcinogen dose. These alterations, however, a peared to coincide with the development of tumors and we not observed in animals with premalignant lesions. Levels chemical carcinogens that were capable of inducing tumo did not necessarily suppress the immune response. (23 refs

78-5087 **Genetics of Susceptibility in t Platyfish/Swordtail Tumor System to Develo Fibrosarcoma and Rhabdomyosarcoma Following Treatme with N-Methyl-N-nitrosourea (MNU).** (Eng) Schwab, M (Genetisches Institut, Justus-Liebig-Universitat Giesse Heinrich-Buff-Ring 58-62, D-6300 Giessen, W. Germany Abdo, S.; Ahuja, M. R.; Kollinger, G.; Anders, A.; Ander F.; Frese, K. *Z Krebsforsch* 91(3): 301-315; 1978.

The susceptibility (S) of 65 genotypes of xiphophorine fish (platy and swordtail fish) to the development of mesenchymal tissue neoplasms [fibrosarcomas (Fi) and rhabdomyosarcomas (Rh)] was tested following treatment of 7,000 fish with N-methyl-N-nitrosourea (MNU). The fish were given four 1-hr treatments with 10^{-3} M MNU at 2-wk intervals. The degree of S to the development of Fi and Rh varied considerably, ranging from zero in certain genotypes to almost 9% in others. This suggests that the degree of S is determined by the genetic constitution of the animal. An S that was high and reproducible was obtained only in backcross generations resulting from *Platypoecilus variatus/Xiphophorus helleri* hybrids and *X. helleri* as the recurrent parent. Purebred species of *P. variatus* and *X helleri* and their F_1 progeny were not susceptible. The differential S may be a function of the type of control of a tumor gene (*Tu-Fi-Rh*) endogenous to *P. variatus* and involved in the development of Fi and Rh. In *P. variatus* and in the F_1 offspring, the *Tu-Fi-Rh* gene is controlled by repressing genes (*R* genes) linked and not linked to *Tu-Fi-Rh*. Because simultaneous mutation of both *R* genes after MNU treatment is extremely unlikely, these genotypes have an extremely low S. In the backcross hybrids, however, the unlinked *R* gene is eliminated and only the linked *R* gene remains. This condition confers a high degree of S, because one single mutation may lead to impairment of this *R* gene and to the *Tu-Fi-Rh*-mediated formation of Fi and Rh. It is concluded that in xiphophorine fish, S to the development of MNU-induced Fi and Rh is related directly to the genotype. (60 refs)

78-5088 **Enhanced Development of Mammary Tumors in Rats Following Transplacental and Neonatal Exposure to Ethylnitrosourea.** (Eng) Mandybur, T. I. (Dept. Pathology, Univ. Cincinnati Medical Coll., Medical Sciences Building, 231 Bethesda Ave., Cincinnati, OH, 45267); Ormsby, I.; Buncher, C. R. *Cancer Res* 38(10): 3182-3185; 1978.

The transplacental and neonatal induction of mammary tumors (MT) in Sprague-Dawley rats by ethylnitrosourea (ENU) was investigated. Six experimental groups were used: (1) untreated controls, (2) rats treated transplacentally (T) on days 16 or 17 of gestation with 1 ml/kg trioctanoin; (3) rats treated T on day 16 or 20 of gestation with 10 mg/kg ENU ip; (4) rats treated on day 4, 5, or 7 of life with 30 mg/kg ENU ip; (5) rats treated T with 60 mg/kg ENU; and (6) rats treated T with 120 mg/kg ENU. Tumors developed in 10/35 Group 1, 9/21 Group 2, 4/48 Group 3, 14/25 Group 4, 25/63 Group 5, and 4/9 Group 6 animals. The median tumor induction time decreased steadily from 17.5 mo in Group 1 to 4.5 mo in Group 6. Several tumors from each group were examined histologically; the numbers of benign (B) and malignant (M) tumors in each group were as follows: Group 1 5B, 3M; Group 2 6B, 3M; Group 3 2B, 2M; Group 4 1B, 8M; Group 5 6B, 17M; Group 6, 1B 6M. Sarcomas were observed only in Groups 1 and 3; carcinomas predominated in the high-dose ENU groups. Tumors developed mostly in females. Approx 88% of the MT-bearing rats in Groups 4, 5, and 6 MT also had neurogenic tumors. It is concluded that transplacental and neonatal exposure to ENU induces mammary carcinogenesis in susceptible animals. (19 refs.)

78-5089 **Scanning Electron Microscopy of Cloned Astrocytic Lines Derived from Ethylnitrosourea-induced Rat Gliomas.** (Eng) Spence, A. M. (Div. Neurology, RG-20, Univ. Washington, Seattle, WA, 98195); Coates, P. W. *Virchows Arch Cell Pathol* 28(1): 77-85; 1978.

Six cloned astrocytoma cell lines derived from four ethylnitrosourea-induced F-344 rat gliomas (36B, spinal malignant astrocytoma; 40A, cerebral malignant astrocytoma; 44B, spinomedullary astrocytoma; and 48A, cerebral glioblastoma multiforme) were examined in vitro by scanning electron microscopy (SEM). Two of these lines were further examined in vivo after intracerebral transplantation into syngeneic, sex-matched rats. All clones consisted of stellate cells that were reasonably homogeneous within individual glioma lines. The surface features of the lines tended to be rough. They were marked by the presence of microvilli mainly on cell bodies, rounded elevations, miniridges, ruffles, occasional blebs, and filopodia projecting from cell processes. The degree of cell membrane roughness varied among the lines. Line 40A-2 showed an extreme degree of microvillous formation and ruffling that correlated with a short cell-doubling time. Line 36B-10 was intermediate between line 40A-2 and the other lines, which showed fewer microvilli, ruffles, and filopodia. These features of lines 40A-2 and 36B-10 were maintained after transplantation into brain. The distinct variations in the cell membrane topography in these tumors are thought to be unrelated to their species of origin or mode of genesis (spontaneous, virally, or chemically induced). (20 refs.)

78-5090 **Selective Induction of Melanomas in Gerbils (*Meriones unguiculatus*) Following Postnatal Administration of N-Ethyl-N-nitrosourea.** (Eng) Kleihues, P. (Pathologisches Institut, Klinikum der Albert-Ludwigs-Universitat, 7800 Freiburg, W. Germany); Bucheler, J.; Riede, U. N. *J Natl Cancer Inst* 61(3): 859-863; 1978.

Following a single ip injection (50 mg/kg) of N-ethyl-N-nitrosourea (ENU) on postnatal day 7 or 20, 9/21 gerbils developed a total of 15 cutaneous melanomas. The mean survival time of tumor-bearing animals was 909 ± 212 days. Neoplasms were preferentially located at sites with little hair and with a high content of pigment cells (feet, ears, tail, or snout). Histologic studies of newborn gerbils indicated that ENU-induced malignant transformation occurred in differentiated melanocytes rather than in precursor cells of the neural crest. (21 refs.)

78-5091 **Changes in Surface Morphology Related to Ethyl-nitrosourea-induced Malignant Transforma-**

tion of Cultured Rat Brain Cells (Meeting Abstract). (Eng) Roscoe, J. P. (Sch. Pathology, Middlesex Hosp. Medical Sch., London, England); Winslow, D. P.; Rowles, P. *Br J Cancer* 38(1): 192; 1978. (no refs)

78-5092 **In Vitro Malignant Transformation of Fetal Brain Cells Exposed In Uterus to Ethylnitrosourea (ENU) (Meeting Abstract).** (Eng) Yoshida, J. (New York Univ. Medical Center, New York, NY); Cravioto, H.; Ransohoff, J. *J Neuropathol Exp Neurol* 37(5): 711; 1978. (no refs)

78-5093 **Effect of Dibutyryl Cyclic AMP on Rat Tumorgenesis by Ethylnitrosourea (Meeting Abstract).** (Eng) Nagai, M. (Dept. Neurosurgery, Dokkyo Univ. Sch. Medicine, Mibu, Tochigi, Japan); Arai, T.; Awa, H. *J Neuropathol Exp Neurol* 37(5): 664; 1978. (no refs)

78-5094 **Induction of Malignant Tumors in Wistar and Sprague-Dawley Rats by Single Doses of n-Butyl-nitrosourea in Perinatal and Juvenile Phases of Development.** (Ger) Zeller, W. J. (Deutsches Krebsforschungszentrum, Institut fur Toxikologie und Chemotherapie, Im Neuenheimer Feld 280, D-69 Heidelberg 1, W. Germany); Ivankovic, S.; Zeller, J. *Arch Geschwulstforsch* 48(1): 9-16; 1978.

n-Butylnitrosourea (BNU: 120 mg/kg po, ip, or sc) was given to pregnant Wistar rats on day 22 postconception (pc); the same dose was injected in the interscapular region of fetuses delivered surgically on day 22 pc, 1- and 2-day-old Wistar rats, and 10- and 30-day-old Sprague-Dawley rats. In 50% of the progeny, tumors (mainly neurogenic) developed both after diaplacental and direct application of BNU on day 22 after conception. After neonatal application, tumors (almost exclusively neurogenic) were found in >85% of the treated animals. Comparison of survival time and tumor rates among the various groups revealed that the nervous tissue of the rat is less sensitive to BNU prenatally than in the neonatal phase of development. After application of BNU to 10-day-old rats, >95% of the animals developed neurogenic tumors almost exclusively, and there was a high percentage of brain tumors. There was a significant increase in survival time and a decrease in total tumor yield in rats treated at age 30 days. There was also a decrease in the rate of neurogenic tumors and an increase in tumors outside the nervous system. Single doses of BNU were not leukemogenic in the late prenatal and neonatal phase: only 2/154 animals developed leukemia. Following BNU treatment of 30-day-old rats, leukemia was diagnosed in 7/40. However, this increased incidence in 30-day-old rats over that seen in younger rats was not considered significant. (21 refs.)

78-5095 **Involvement of Chromosome #2 in Chromosome Changes in Primary Leukemia Induced in Rats by N-Nitroso-N-butylurea.** (Eng) Uenaka, H. (Dept Pathology, Kobe Univ. Sch. Medicine, Ikuta-ku, Kobe 650 Japan); Ueda, N.; Maeda, S.; Sugiyama, T. *J Natl Cancer Inst* 60(6): 1399-1404; 1978.

Cytogenetic studies were made of 34 primary leukemias induced in outbred Long-Evans rats by N-nitroso-N-butylurea (NBU: 0.04% in drinking water for 125 days, beginning at age 7 wk). The results revealed leukemia cells with No. 2 trisomy and a long No. 2 chromosome, changes that are characteristic of the leukemias induced by polycyclic hydrocarbon carcinogens such as 7,12-dimethylbenz(a)anthracene and 7,8,12-trimethylbenz(a)anthracene. These findings suggest a common mode of action of different carcinogenic chemicals at the chromosome level, although the lower incidence of these chromosome changes and of erythroblastic leukemias with NBU implies subtle differences in their actions. (26 refs.)

78-5096 **Studies on N,N′-Dimethylnitrosourea-induced Brain Tumors in Rats--Especially, on Microtumors.** (Eng) Jinnai, H. (Dept. Pathology, Okayama Univ Medical Sch., Okayama 700, Japan). *Acta Med Okayama* 32(2): 119-137; 1978.

A study was made of the incidence, distribution, and histopathology of tumors induced by N,N′-dimethylnitrosourea (DMNU) in the brains of Sprague-Dawley rats. The rats were inoculated sc, in the interscapular region, with 40 mg/kg/wk of DMNU; rats were sacrificed 24 hr after 1, 5, or 10 injections or after 150-246 days (total, 17-21 injections). Animals sacrificed after 1-10 injections showed no pathological changes in any organs. Between 157 and 246 days, however, 122 gliomas developed in 38/55 rats. Sixty-six microtumors (diameter <1 mm) were detected in 28/38 rats by light microscopic observation of serial sections. The microtumors were of three types: oligodendrogliomas (55 tumors, 30 of which developed in the corpus callosum), astrocytomas (8 tumors, 5 of which were in the cerebral cortex), and mixed gliomas (3 tumors). Anaplasia occurred as tumors became larger, and cellular atypism was observed in 11/56 enlarged tumors. The target cells of DMNU were well-differentiated glial cells that had migrated from the matrix layer. (25 refs.)

78-5097 **The Relationship Between Mutagenicity and Carcinogenicity of Some Nitrosamines.** (Eng) Andrews, A. W. (Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21501); Thibault, L. H.; Lijinsky, W. *Mutat Res* 51(3): 319-326; 1978.

The mutagenicity of 4 nitrosotrialkylureas, 8 aliphatic nitrosamines, and 14 cyclic nitrosamines was determined using the Ames *Salmonella typhimurium* assay, and the results

were compared with existing carcinogenicity data. There was agreement between the mutagenicity and carcinogenicity data for 80% of the compounds and a lack of agreement for 20%. The Ames test failed to detect 3/22 carcinogens among the 26 nitrosamines tested. Until this or some other test demonstrates a quantitative and qualitative correlation between mutagenic potency and carcinogenic potency, it will be difficult to establish a hierarchy of carcinogenic risk among a group of compounds such as the nitrosamines. (16 refs.)

78-5098 **Neoplastic Transformation of Human Diploid Fibroblast Cells by Chemical Carcinogens.** (Eng) Kakunaga, T. (Chemistry Branch, NCI, Bethesda, MD, 20014). *Proc Natl Acad Sci USA* 75(3): 1334-1338; 1978.

The ability of 4-nitroquinoline 1-oxide (4NQO) to transform KD fibroblasts derived from a cutaneous punch biopsy of a normal human adult was investigated. Alterations of the cell growth pattern such as higher density and piling up of cells were noticed in some fractions of cultures that were successively subcultured after 4NQO treatment (0.1 μg/ml). Morphologically altered cells retained this growth pattern and became established lines of transformed cells without showing the limited life-span characteristic of normal cells in culture. The transformed cells showed a higher saturation density and the ability to grow in soft agar. It is doubtful that selection of preexisting transformed human cells was the mechanism of transformation, because clones of these normal cells could also be used to assess the transforming effect of 4NQO. Preliminary studies suggested that numerous cell divisions were required for the development of transformation. Female nude mice were inoculated sc with 0.2 or 2.0 x 10^6 transformed cells, and solid tumors appeared at the injection site after an av latent period of 6 wk. Treatment of cells with 0.1 μg/ml N-methyl-N′-nitro-N-nitrosoguanidine induced transformation in a manner similar to that following 4NQO treatment. However, transformation was not induced with 4-aminoquinoline 1-oxide, 3-methylcholanthrene (a carcinogen that cannot be metabolically activated by the target cells employed), or dimethyl sulfoxide (the solvent used in the experiments). (20 refs)

78-5099 **Carcinogenicity of Quinoline and Its Derivatives in Rat (Meeting Abstract).** (Eng) Shirai, T. (Nagoya City Univ. Medical Sch., 4-35 Mizoho-cho, Miguho-ku, Nagaya-shi, Aichi-ku, Japan); Fukushima, S.; Murasaki, G.; Ogiso, T.; Takahashi, M.; Ito, N. *In: Summary Program and Abstracts of Papers. Proceedings of the 3rd Asian Cancer Conference Held by the Philippine Cancer Society under the Auspices of the Asian Federation of Organizations for Cancer Research and Control in Manila, 26-30 September, 1977.* Philippine Cancer Society. (Manila, Philippines): 184 pp.; 109-110; 1977. (no refs)

78-5100 **Binding of Polynucleotides with 4-Nitrosoquinoline 1-Oxide Producing the Same Free Radical as That Produced from 4-Hydroxyaminoquinoline 1-Oxide.** (Eng) Kodama, M. (Biophysics Div., Natl. Cancer Center Res. Inst., Tsukiji 5-1-1, Chuo-ku, Tokyo 104, Japan); Nagata, C.; Mochizuki, M.; Okada, M. *Gann* 69(2): 285-286; 1978.

Evidence is presented that 4-nitrosoquinoline 1-oxide (4-NOQO) produces the same free radical as that produced from 4-hydroxyaminoquinoline 1-oxide (4-HAQO) and that 4-NOQO binds it covalently with polynucleotides. 4-NOQO was soluble in dioxan, ethanol, and dimethyl sulfoxide, and it gave an electron spin resonance (ESR) signal with a fine structure of six lines. After the dioxan soln of 4-NOQO it was degassed, the signal was further resolved into hyperfine structure of 52 lines, which was the same signal as that observed after a dioxan soln of 4-HAQO was degassed. The free radical thus formed showed no decay, even after standing at room temperature for 3 days under anaerobic conditions. In contrast, the ESR signal from 4-HAQO decayed progressively. Thus, the free radical produced from 4-HAQO was formed by oxidation, but that formed from 4-NOQO was produced by reduction. The addition of a reducing agent such as sodium borohydride to the dioxan soln of 4-NOQO resulted in a marked increase in the ESR signal, whereas the same treatment decreased the signal in the 4-HAQO soln. Both 4-NOQO and 4-HAQO were sufficiently active to bind poly(G) without activation, the former being more active than the latter. The emission spectra of poly(G)-bound 4-NOQO and 4-HAQO showed max peaks at 450 nanometers; these peaks coincided with the emission spectrum of DNA isolated from 4-HAQO-treated cells. (7 refs)

78-5101 **Carcinogenic Effect of N-Methyl-N′-nitro-N-nitrosoguanidine (MNNG) in European Hamsters.** (Eng) Ketkar, M. (Abteilung fur Experimentelle Pathologie, Medizinische Hochschule Hannover, Karl-Weichert-Allee 9, 3000 Hannover 61, W. Germany); Reznik, G.; Green, U. *Cancer Lett* 4(4): 241-244; 1978.

The effects of chronic administration of N-methyl-N′-nitro-N-nitrosoguanidine (MNNG) on European hamsters of both sexes were determined. The LD_{50} was 1,378 mg/kg for males and 1,070 mg/kg for females. One-tenth of the LD_{50} was administered in water by stomach tube once weekly for 20 wk to 10 animals of each sex. Av survival for males and females was 21 and 18 wk, respectively. Papillary hyperplasia and hyperkeratosis of the forestomach occurred in nearly all hamsters. The epithelium of the upper digestive tract was often thickened, and hemorrhages were noted in the intestine. Controls did not show neoplastic alterations. The earliest time to tumor appearance was 13 wk for males and 20 wk for females; av tumor latency was 25 wk. Tumor incidence was 80% in males, 30% in females. Eight males and three females developed multiple squamous cell papillomas of the forestomach with various degrees of keratinization. Invasive

squamous cell carcinomas of the forestomach were noted in in three males and one female; invasion extended to the duodenum, small intestine, spleen, liver, and pancreas. In addition, fibrosarcomas of the forestomach (1 male) and glandular stomach (1 male) glandular stomach (1 male) were found. In males, tumors at other sites included 2 squamous cell papillomas of the pharynx, 2 squamous cell papillomas of the nasal cavity, 1 squamous cell carcinoma invading the nasal septum, and 1 squamous cell papilloma of the trachea. Females hamsters had no neoplastic growths in the nasal cavities, but they occasionally had hyper- and metaplastic epithelial changes. Two females did, however, develop invasive squamous cell papillomas of the larynx. (9 refs)

78-5102 **Pathways of Mutagenesis and Repair in *Escherichia coli* Exposed to Low Levels of Simple Alkylating Agents.** (Eng) Schendel, P. F. (Imperial Cancer Res. Fund, Mill Hill Labs., London NW7 1AD, England); Defais, M.; Jeggo, P.; Samson, L.; Cairns, J. *J Bacteriol* 135(2): 466-475; 1978.

Repair processes induced in *Escherichia coli* strains following exposure to ethyl methane sulfonate, methyl methane sulfonate, and N-methyl-N′-nitro-N-nitrosoguanidine were studied to determine whether error-prone (*lexA*-dependent) or *lex*-independent repair occurs. Bacterial strains were incubated with various concentrations of the mutagens. Error-prone repair was responsible for the majority of mutants formed after a large dose of alkylating agent, but the results suggest that this repair probably does not contribute significantly to mutagenesis at low concentrations of these chemicals. The mutagenicity at low doses was reduced by a repair system constitutively present in *lexA* cells but absent in *lexA* mutants. This system reduced mutagenesis until a second error-free system, called the adaptive response, could be induced. The adaptive response was capable of dealing with a much larger amount of alkylation damage than the constitutive system, and it appeared to reduce mutagenesis by both decreasing the number of sites available for mutagenesis and delaying the induction of error-prone repair enzymes. Based on these observations, a model for chemically induced mutagenesis is discussed that maintains that the observed mutation frequency is dependent on a competition between these two error-free systems and the two mutagenic pathways. (29 refs.)

78-5103 **A Possible Process of Conversion of Food Components to Gastric Carcinogens.** (Eng) Endo, H. (Cancer Res. Inst., Faculty Medicine, Kyushu Univ., Fukuoka 812, Japan); Ishizawa, M.; Endo, T.; Takahashi, K.; Utsunomiya, T.; Kinoshita, N.; Hidaka, K.; Baba, T. *In: Human Risk Assessment. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Boo C), 583 pp.; 1591-1607; 1977.

A possible process for the conversion of food components t gastric carcinogens was tested in order to identify causal fa tors for human gastric cancer. N-Methyl-N′-nitro-N-n troguanidines (MNNG) was selected as a model carcinoge and MNNG-like compounds among food were componen surveyed. Fifteen naturally occuring guanidine derivativ were selected; these compounds are similar in structure t N-methyl-N′-nitroguanidines (MNG), which yields MNN by nitrosation under strong acidic conditions. Only methy guanidine (MG) showed mutagenicity in the *Salmonella t phimurium* assay after nitrosation in gastric juice (pH 1.2 This compound was not mutagenic when nitrosated at pH > 3.4. Methylnitrosocyanamide (MNC), which was ident fied as the mutagenic principle of nitrosated MG, was 1 times more mutagenic than MNNG; however, the mutageni quality of both compounds was similar. The in vitro yield MNC formed from MG and nitrite in gastric juice (pH 1.2) was 0.3%-0.5%; the in vivo yield was 6%-10% of the i vitro yield. MNC was much more labile in gastric juice tha MNG, and it lost its activity quickly. When given po to rat with the drinking water MNC was strongly carcinogenic t the forestomach and esophagus and less carcinogenic in th glandular stomach. The production of nitrite from nitrate b the oral microflora has been estimated to be 10 mg/day. Sinc the daily amount of saliva swallowed is 1.5 liters, saliva ma be the most important source of nitrite. (53 refs)

78-5104 **Reticulum Cell Sarcoma Production in Masto mys by Oral Administration of N-Methyl-N′ Nitro-N-Nitrosoguanidine (MNNG) (Meeting Abstract)** (Eng) Kamano, T. (Gastroenterology, Dept. Surgery, Junten do Univ. Hosp., Hongo, Bunkyu, Tokyo, Japan); Kawasaki M.; Kodama, T.; Kishino, H.; Kidokoro, T.; Kurihara, M *In: Summary Program and Abstracts of Papers. Proceeding of the 3rd Asian Cancer Conference Held by the Philippin Cancer Society under the Auspices of the Asian Federation o Organizations for Cancer Research and Control in Manila, 26-30 September, 1977.* Philippine Cancer Society. (Manila, Philippines): 184 pp.; 75-76; 1977. (no refs)

78-5105 **The Transformation of Human Diploid Cells by Chemical Carcinogens.** (Eng) Kakunaga, T. (Chemistry Branch, NCI, NIH, Bethesda, MD, 20014). *In: Human Risk Assessment. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book C), 583 pp.; 1537-1548; 1977.

The in vitro transformation of human diploid cells by chemical carcinogens is reported. The cells were derived from a skin

biopsy of a normal woman who did not show any sign of genetic disease. They were exposed to 4-nitroquinoline-1-oxide (4NQO), 4-aminoquinoline-1-oxide (4AQO), N-methyl-N′-nitro-N-nitrosoguanidine (MNNG), or 3-methylcholanthrene (3-MC). Before treatment, the cells exhibited the typical morphology of fibroblast cells with no evidence of an epitheliallike morphology. Assays in which cells were (1) treated with 0.01-1.0 μg/ml 4NQO or MNNG and then plated to form individual colonies; (2) maintained at confluence after treatment; or (3) treated, allowed to divide for four or five generations, and plated in agar failed to reveal any transformation. However, cells that were treated with 4NQO or MNNG for 30 min and then subcultured at 1:4 dilutions whenever they became confluent showed transformed foci after 5-10 passages. Morphologically altered cells were found in a small area of a very small number of dishes. The main alteration was the formation of an area with a high density of cells showing frequent mitosis. Transformed foci were not observed in cultures treated with 3-MC or 4AQO. Apparently, an av of at least 13 cell divisions is necessary for the transformation of human diploid cells. The transformed cells had an increased saturation density and an increased ability to grow in soft agar, and they grew exponentially. Treated, untransformed cells did not exhibit these characteristics. Transplantation of the transformed cells into nude mice resulted in tumors at the site of injection within 2-21 wk, depending on the cell line and the number of cells inoculated. Spontaneous tumor regression was observed in only one case. No tumors were produced by injection of morphologically unaltered cells. (17 refs.)

78-5106 **A Radioimmunoassay for O^6-Alkyl Guanine Derivatives (Meeting Abstract).** (Eng) Kyrtopoulos, S. A. (Courtauld Inst. Biochemistry, Middlesex Hosp. Medical Sch., Middlesex, England); Swann, P. F. *Br J Cancer* 38(1): 170; 1978. (1 ref)

78-5107 **Interaction of 9-Aminoacridine with 7-Methylguanosine and 1,N^6-Ethenoadenosine Monophosphate.** (Eng) Kubota, Y. (Dept. Chemistry, Yamaguchi Univ., Yamaguchi 753, Japan); Nakamura, H.; Morishita, M.; Fujisaki, Y. *Photochem Photobiol* 27(4): 279-481; 1978.

The fluorescence properties of 9-aminoacridine (9AA) in aqueous solns of 7-methylguanosine (7MeG) and 1,N^6-ethenoadenosine monophosphate (eAMP) were investigated to obtain information on the interaction between 9AA and DNA bases. The fluorescence of 9AA was quenched by 7MeG and eAMP as well as by unmodified bases such as guanosine monophosphate and AMP. Both dynamic and static quenching processes were involved. (14 refs)

78-5108 **Phosphate Diester Formation Following Reaction of β-Propiolactone with Thymidine-5′-monophosphoric Acid.** (Eng) Segal, A. (Lab. Organic Chemistry and Carcinogenesis, Inst. Environmental Medicine, New York Univ. Sch. Medicine, New York, NY, 10016); Mate, U.; Wortman, M. *Chem Biol Interact* 21(2/3): 249-261; 1978.

The carcinogen β-propiolactone (BPL) was reacted with thymidine-5′-monophosphoric acid (dThd5′P, or TMPA) at pH 1.8 and at 24-76 C to determine whether BPL forms phosphodiesters with TMPA. Acidic conditions were chosen to try to avoid complicating ring alkylations. At 37, 50, 63, and 76 C, the reactions produced unreacted TMPA, which represented 90% of the UV-absorbing material (UVAM) on paper chromatograms, and a product designated compound F2, which represented 10% of the UVAM; at 24 C, F2 represented 5% of the material. The identical UV spectra of TMPA and F2 at pH 1 and 13 ruled against ring alkylation; and, on the basis of chemical tests, alkaline phosphatase and snake venom phosphodiesterase (SVPD) treatment at both pH 7.2 and 9.0, and incubation at pH 1, 7, 9, 11, and 13, F2 was assigned the structure 5′-O-(2-carboxyethyl)phosphonothymidine. BPL-TMPA reaction at pH 6.6-7.0 produced two additional compounds, F3 and F4. The UV spectra of TMPA, F3, and F4 were identical at pH 1 and 13. TMPA represented 36% of the UVAM, the remainder being F2 (36%), F3 (24%), and F4 (4%). F3 contained BPL and it was a phosphodiester, since treatment of F3 with SVPD at pH 7.2 or 9.0 resulted in its complete conversion to TMPA. A tentative assignment of a structure containing a six-membered ring phosphate ester-acyl phosphate derivative was assigned to F3. Results of BPL-TMPA reactions at pH 7.0-7.5, 7.5-8.0, and 8.0-8.5 were similar to those at pH 6.6-7.0. No ring alkylation was detected. If BPL does form acyl phosphates, a phsophate ester-acyl phosphate cross-link may help to explain the association of nucleic acids and cellular membranes induced by BPL, the intermolecular linking of DNA, and the DNA-protein complexes produced by BPL. These phenomena could be responsible for abnormal gene expression leading to neoplasia. (49 refs.)

78-5109 **Oral Toxicity of 1,1-Dichloroethylene in the Rat: Effects of Sex, Age, and Fasting.** (Eng) Andersen, M. E. (Toxicology Detachment, Naval Medical Res. Inst., Wright-Patterson Air Force Base, OH, 45433); Jenkins, L. J. *Environ Health Perspect* 21: 157-163; 1977.

The acute po toxicity of 1,1-dichloroethylene (1,1-DCE; vinylidene chloride) was investigated in male and female Holtzman HOT:(SD)BR rats of various sizes. When fasted and fed large, mature, male rats were given 400 mg 1,1-DCE, the hepatotoxic response was four to five times greater in the fasted rats. Determinations of the po LD_{50} of male rats indictated that for large animals (395 g), mortality increased monotonically from 0% to 100% as the dose increased from 800 to 2,000 mg/kg; the estimated acute LD_{50} was similar to that reported previously, 1,550 mg/kg. With males weighing 224 g, mortality varied between 10% and 33% following

doses of 50-800 mg/kg 1,1-DCE. With rats weighing 73 g, 100% mortality was noted at 300 mg/kg; percent mortality then decreased as the dose was increased up to 800 mg/kg. Maxima and extended plateaus were seen in the survival curves of all males between doses of 100 and 700 mg/kg, making it impossible to calculate an exact LD_{50}. Following a dose of 50 mg/kg, mortality and hepatotoxicity were greatest in rats weighing 100-150 g; smaller and larger males were less susceptible. Female rats did not show this variation in susceptibility with size, and they were less susceptible to the toxic effects of 1,1-DCE: the threshold of toxicity in male rats of 100-150 g occurred near 50 mg/kg, while for females it was closer to 100 mg/kg. These findings suggest that 1,1-DCE is metabolized to a toxic intermediate by some saturable pathway. Based on the effects of pretreatment with microsomal enzyme inhibitors and activators on 1,1-DCE toxicity in rats of various sizes, it appears that there are at least two microsomal reactions involved in 1,1-DCE metabolism. (25 refs)

78-5110 **Hepatic Macromolecular Binding Following Exposure to Vinyl Chloride.** (Eng) Watanabe, P. G. (Toxicology Res. Lab., Health and Environmental Res., 1803 Building, Dow Chemical Co., Midland, MI, 48640); Zempel, J. A.; Pegg, D. G.; Gehring, P. J. *Toxicol Appl Pharmacol* 44(3): 571-579; 1978.

Male Sprague-Dawley rats were exposed by inhalation to 1, 25, 50, 250, 1,000, or 5,000 ppm ^{14}C-labeled vinyl chloride (VC) for 6 hr, and covalent binding of VC to hepatic macromolecules and nucleic acids was studied to determine if VC-induced carcinogenesis might be related to electrophilic alkylation of macromolecules in vivo. The total amount of VC metabolized and hepatic glutathione content (GSH) content were also measured. The total amount of radioactivity bound to hepatic macromolecules did not increase proportionately to the increase in the exposure concentration of VC, but it was related directly to the total amount of VC metabolized. At exposure concentrations $>$ 50 ppm, the total metabolism of VC and covalent binding appeared to correlate with the induction of hepatic angiocarcinomas in the rats. Isolation of RNA and DNA by a nondigestive procedure from the liver of rats exposed to 1, 100, 250, and 1,000 ppm VC failed to reveal any detectable radioactivity. Hepatic GSH was depressed significantly only at $\geq$ 100 ppm, suggesting that VC carcinogenicity is related to a decreased ability to detoxify the reactive metabolites of VC. The results do not associate the carcinogenic effect of VC with a disproportionate increase in binding of electrophilic metabolites of VC to hepatic macromolecules as the exposure concentration is increased. Moreover, the lack of preferential binding of the metabolites to the hepatocyte nucleic acids suggests that the carcinogenicity of VC may not be associated directly with this commonly accepted mechanism of carcinogenesis. (27 refs.)

78-5111 **Biochemical Effects of Acrylonitrile on the Rat Liver, As Influenced by Various Pretreatments of the Animals.** (Eng) Duverger-van Bogaert, M. (Lab. Biotoxicology, Univ. Louvain, Sch. Pharmacy, UCL-73-69, B-1200 Brussels, Belgium); Lambotte-Vandepaer, M.; Noel, G.; Roberfroid, M.; Mercier, M. *Biochem Biophys Res Commun* 83(3): 1117-1124; 1978.

The effects of acrylonitrile (AN) on the liver enzymatic systems of adult male Wistar rats were studied. The activities of two marker enzymes of the endoplasmic reticulum, glucose-6-phosphatase and NADPH:cytochrome c reductase, were nonsignificantly lowered by treatment of the rats with 10 mg/kg AN ip. AN did not affect the integrity of the liver mitochondria or lysosomes or the levels of SGOT, SGPT, or lipid peroxidation. A dose-dependent increase in lactate dehydrogenase (LDH) and sorbitol dehydrogenase (SDH) levels induced by AN was enhanced by pretreatment with diethyl maleate (DEM) and suppressed by pretreatment with phenobarbital (PB), 3-methylcholanthrene (3-MC), Aroclor 1254, or L-cysteine. Surprisingly, however, AN inhibited 3-MC-induced increases in LDH and SDH. A non-dose-dependent decrease in cytochrome P-450 levels and in the activity of aldrin oxide synthetase was unaffected by DEM and inhibited by PB, 3-MC, Arochlor 1254, and L-cysteine. AN did not significantly decrease the Km of aldrin oxide synthetase. Propionitrile (10 mg/kg) also increased the levels of SDH and LDH, but it had no effect on cytochrome P-450 or aldrin oxide synthetase. (25 refs.)

78-5112 **Intermediate Metabolites of Thiocarbamides, Thioureylenes and Thioamides: Mechanism of Formation and Reactivity.** (Eng) Ziegler, D. M.(Clayton Foundation Biochemical Inst., Univ. Texas at Austin, Austin, TX, 78712). *Biochem Soc Trans* 6(1): 94-96; 1978.

The formation of the intermediate metabolites of thiocarbamides, thioureylenes, and thioamides was investigated in vitro. Studies with microsomal amine oxidases and the thiocompounds indicated that only micromolar concentrations of the latter were required to half-saturate the oxidase; at saturation, all compounds were oxidized at rates equal to those observed with tertiary amine substrates. However, unlike the tertiary amines, 2 moles each of oxygen and NADPH were consumed per mole of substrate oxidized, which indicates that the oxidase catalyzes the dioxygenation of sulfur-containing compounds. Dioxygenations catalyzed by a monooxygenase can occur by sequential enzymic oxidation of the initial substrate through a monooxygenated intermediate or by disproportion of the intermediate. Although in vitro experiments demonstrated that thiocarbamides and thioureylenes can be oxidized to sulfenic and sulfinic acids, it is unlikely that either metabolite could be formed in vivo, because the acids are rapidly reduced to the parent compound by glutathione. The reduction can lead to a cycle that would operate until the NADPH or oxygen became limiting. In vivo hamster experiments indicated that at toxic doses, the cycle is terminated by the loss of glutathione: glutathione content

n the liver, lung, and bone marrow of methimazole-reated animals decreased in a time- and dose-dependent nanner. It is suggested that the toxicity of thiocarba-nides and thioureylenes may be partly due to their bility to oxidize glutathione. (11 refs)

78-5113 **Enhancement of DL-Ethionine-induced Liver Carcinogenesis in Rats Fed a Choline-devoid Diet.** (Eng) Shinozuka, H. (Dept. Pathology, Univ. Pitts-burgh Sch. Medicine, Pittsburgh, PA, 15261); Lombardi, B.; Sell, S.; Iammarino, R. M. *J Natl Cancer Inst* 61(3): 813-817; 1978.

The effects of a choline-devoid (CD) or a choline-supple-nented (CS) diet on the induction of liver tumors in male Sprague-Dawley rats by DL-ethionine were determined. Groups of rats were fed a plain CD or a plain CS diet, or the same diets containing 0.05% DL-ethionine. Rats were killed after 14, 22, or 30 wk and the livers were examined. In rats fed the CD plus ethionine diet, hepatocellular carcinomas developed in 3/6 rats examined at 14 wk, 13/16 seen at 22 wk, and 6/8 seen at 30 wk. No liver tumors were noted in any of the other groups. The absolute food and ethionine intake of the rats receiving the CS plus ethionine diet was approx twice that of those fed ethionine plus the CD diet. Thus, the latter developed tumors despite the ingestion of less ethionine and a lower caloric intake. These findings suggest that a CD diet alters the response of rat liver to ethionine and leads to an early and enhanced induction of hepatocellular carcinoma. (28 refs.)

78-5114 **Synthesis, DNA-Binding and Biological Activity of a Double Intercalating Analog of Ethidium Bromide.** (Eng) Kuhlmann, K. F. (Bio-Organic Chemistry Dept., Life Sciences Div., SRI International, Menlo Park, CA, 94025); Charbeneau, N. J.; Mosher, C. W. *Nucleic Acids Res* 5(7): 2629-2641; 1978.

The synthesis and DNA-binding characteristics of a bis[6-(3-substituted phenyl)] phenanthridinium salt and its monomeric analog are reported. Evidence provided by UV and circular dichroism spectra, thermal denaturation profiles, and equilibrium dialysis of the drug-DNA complex led to the conclusion that both phenanthridine moieties intercalate in the helix. The double intercalator appears to be less potent than ethidium chloride as an inhibitor of nucleic acid synthesis in cultured L1210 cells, although it is more potent than a monomeric analog. The low potency may be due to a low cell influx rate. (30 refs.)

78-5115 **The Mutagenicity and Cytotoxicity of Selenite, "Activated" Selenite and Selenate for Normal and DNA Repair-deficient Human Fibroblasts.** (Eng) Lo, L. W. (Cancer Res. Centre, Univ. British Columbia, Vancouver, Canada); Koropatnick, J.; Stich, H. F. *Mutat Res* 49(3): 305-312; 1978.

At doses of 8×10^{-5} to 3×10^{-3} M, sodium selenite (Na_2SeO_3) induced DNA fragmentation, DNA-repair synthesis, chromosome aberrations, and a mitotic inhibition in cultured human fibroblasts. The response of DNA repair-deficient xeroderma pigmentosum (XP) fibroblasts to selenite was comparable to that of control cells. Incubation with mouse liver S-9 microsomal fraction enhanced the lethal effect of selenite and increased its ability to induce chromosome aberrations and DNA-repair synthesis. XP cells behaved as control cells when treated with activated selenite. Sodium selenite (Na_2SeO_4) at doses of 8×10^{-5} to 3×10^{-3} M could not be activated by incubation with an S-9 preparation. Selenate induced a small but significant DNA-repair synthesis. (24 refs)

78-5116 **Tumours and Disorders of Porphyrin Metabolism in Rats with Chronic Experimental Lead Poisoning (Meeting Abstract).** (Eng) Zawirska, B. (Inst. Pathomorphology, Medical Sch., Wroclaw, Poland). *J Clin Chem Clin Biochem* 16(1): 56; 1978. (4 refs)

78-5117 **In Vitro Neoplastic Transformation of Syrian Hamster Cells by Lead Acetate and Its Relevance to Environmental Carcinogenesis.** (Eng) Dipaolo, J. A. (Biology Branch, NCI, Bethesda, MD, 20014); Nelson, R. L.; Casto, B. C. *Br J Cancer* 38(3): 452-455; 1978.

Secondary Syrian hamster embryo cell cultures were treated with 0, 1.0 or 2.5 μg/ml lead acetate for 8 days and observed for transformation. A total of 18 transformed colonies were noted in 9 petri dishes treated with 2.5 μg/ml, 9 colonies were noted in the 10 dishes treated with 1.0 μg/ml, and none were noted in the 11 controls. Cells derived from these transformed colonies produced fibrosarcomas when injected sc into Syrian hamsters or nude mice. Primary hamster embryo cultures were treated for 18 hr with varying dilutions of lead acetate, inoculated with 200 focus-forming units of simian adenovirus 7 (SA7), and assayed for enhancement of viral transformation. Cell lethality from the lead acetate treatment was less in this assay, probably because of the short time of incubation and the large number of cells used. Statistically significant enhancement of SA7 transformation was observed with lead acetate doses of 100 and 200 μg/ml. These findings suggest that lead salts may be potential carcinogens for humans. (13 refs.)

78-5118 **Influence of Low Cadmium-Dosages in Subacute Experiments on the Drug Metabolism**

on Mice (Meeting Abstract). (Eng) Abel, J. (Dept. Toxicology, Univ. Duesseldorf, Moorenstrasse 5, D-4000 Duesseldorf, W. Germany); Dieter, H.; Menzel, H.; Ohnesorge, F. K. *Naunyn Schmiedebergs Arch Pharmacol* 302(Suppl): R16; 1978. (no refs)

78-5119 **Carcinogenicity of Nickel Subsulfide for Respiratory Tract Mucosa.** (Eng) Yarita, T. (Dept. Surgery, Inst. Pulmonary Cancer Res., Sch. Medicine, Chiba Univ., Chiba 280, Japan); Nettesheim, P. *Cancer Res* 38(10): 3140-3145; 1978.

The carcinogenicity of nickel subsulfide (Ni_3S_2) was investigated in female Fischer 344 rats bearing sc tracheal transplants from isogenic recipients. Chemical determinations in tracheas treated with 1 and 3 mg Ni_3S_2 indicated that the compound persisted in the trachea for 7 to 9 mo. It showed a marked toxicity for mucociliary epithelium, resulting in widespread atrophy and focal epithelial necrosis during the first 2 mo of exposure. The submucosa showed mononuclear infiltration and signs of fibroblastic and capillary proliferation. In carcinogenesis studies in which 1 mg Ni_3S_2 was implanted in the trachea, tumors were noted in 9/60 tracheas; the first tumor occurred at 11 mo. Of the nine, three were sarcomas and six were carcinomas. The former showed extensive invasion into the host tissues but no distant metastases. Tumors developed in 45/64 tracheas treated with 3 mg Ni_3S_2; the first tumor was observed at 6 mo. Only one of these tumors was a carcinoma, the rest were sarcomas. These findings suggest that, compared with some carcinogenic polycyclic hydrocarbons, Ni_3S_2 may not be a strong carcinogen for the epithelium of conducting airways. However, the carcinoma incidence in the 3 mg group may have been artificially low because of early and high sarcoma incidence; furthermore, the high toxicity of the compound might outweigh its carcinogenicity and result in a misleadingly low carcinoma incidence. (28 refs.)

78-5120 **Gastro-intestinal Tumors in Mice of Three Strains Maintained on Fat-enriched Diets.** (Eng) Szepsenwol, J. (Dept. Biological Sciences, Florida International Univ., Tamiami Trail, Miami, FL, 33144). *Oncology* 35(4): 143-152; 1978.

The effect of fat-enriched diets on the development of primary gastrointestinal tumors was determined in T.M., BALB/c, and C57 Br. mice. Six groups of T.M. mice were treated as follows: (1) controls, regular diet only; (2)-(6) regular diet supplemented with refined corn oil, crude corn oil, refined corn oil + up to 1.5% oleic and linoleic acids, monoolein, and monostearin, respectively. There were two groups of BALB/c and C57 Br. mice, one a control group (7 and 9, respectively) and one fed a diet supplemented with raw egg yolk (8 and 10, respectively). Forestomach tumors (papillomas and squamous cell carcinomas) were found in all mice on fat-supplemented diets, and the incidence varied from group to group: (2) 7/209, (3) 55/196, (4) 97/328, (5) 37/166, (6) 2/155, (8) 10/365, (10) 87/177. The incidence in control groups was very low: (1) 3/195, (7) 0/218, (9) 1/165. In addition, none of the control groups developed pyloric tumors. In the test animals, the incidence of pyloric tumors was highest in Group 10 (27/177) and lowest in Group 2 (2/209) and Group 6 (0/115). None of the control groups and none of the T.M. mice developed intestinal tumors. These tumors were mostly polyps (2/365 in Group 8, 14/177 in Group 10) except for three adenocarcinomas also found in Group 10. The fact that BALB/c and C57 Br. mice developed intestinal tumors but T.M. mice did not may be due to a difference in susceptibility and/or a difference in their diets. It is suggested that cholesterol, levels of which are high in egg yolk, may play an important role in intestinal and gastric tumorigenesis. (33 refs)

78-5121 **A Mutagen in the Feces of Normal Humans.** (Eng) Bruce, W. R. (Ontario Cancer Inst., Toronto, M4X 1K9, Ontario, Canada); Varghese, A. J.; Furrer, R.; Land, P. C. *In: Human Risk Assessment. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book C), 583 pp.; 1641-1646; 1977.

Feces collected from four normal men (25-45 yr old) on full Western diets were assayed for mutagens using the *Salmonella* tester strains TA98, TA100, TA1535, and TA1537 with and without liver microsomes. An agent in the ether extract, E, of many feces was directly active on strains TA100, TA1535, and, to a lesser degree, TA98. The highest activities were usually seen in fraction EBE, a sample derived from E by washing with a basic aqueous solution. Tests with other fractions indicated that there were factors in the water-soluble feces fraction, EBA, that inhibit the expression of mutations. Thus, the actual mutagenicity of a feces sample can be determined only after chemical separation of the active material from the inhibitor. The fecal mutagen was further purified and identified as an N-nitroso compound. Mutagen and nitroso compound levels in the feces of the four donors were reduced by $> 60\%$ when their normal diets were supplemented with ascorbic acid. (5 refs)

78-5122 **Studies on Natural Desmutagens: Screening for Vegetable and Fruit Factors Active in Inactivation of Mutagenic Pyrolysis Products from Amino Acids.** (Eng) Morita, K. (Dept. Induced Mutation, Natl. Inst. Genetics, Misima, Sizuoka-ken 411, Japan); Hara, M.; Kada, T. *Agric Biol Chem* 42(6): 1235-1238; 1978.

Juices from 59 fruits and vegetables were screened for their desmutagenicity to the mutagenic pyrolysis products of

L-citruline, L-lysine, L-ornithine, L-arginine, and L-tryptophan. Mutagenicity assays were carried out with the use of *Salmonella typhimurium* strain TA98 and a rat liver homogenate activating system. Ten samples, those of cabbage, broccoli, green pepper, eggplant, apple, burdock, shallot, ginger, pineapple, and mint leaf, were remarkably effective in inactivating the mutagenicity of L-tryptophan pyrolysis products. Eight others (radish, sweet potato, grape, Japanese ginger, cauliflower, beefsteak plant, enokidake mushroom, and shimeji mushroom) were moderately effective. The other 41 samples were inactive. The 10 effective samples also showed varying degrees of desmutagenicity toward the pyrolysis products of the other amino acids. Three, eggplant, burdock, and broccoli, showed a high degree of desmutagenicity toward all pyrolysis products. The cabbage desmutagenic factor was not affected by ultracentrifugation, dialysis, or treatment with DNase and RNase. It was sensitive to heat (100 C) and to pronase treatment, which suggests that it is a protein. (5 refs.)

78-5123 **Influence of Diets High and Low in Animal Fat on Bowel Habit, Gastrointestinal Transit Time, Fecal Microflora, Bile Acid, and Fat Excretion.** (Eng) Cummings, J. H. (Medical Research Council, Dunn Nutrition Unit, Cambridge, England); Wiggins, H. S.; Jenkins, D. J.; Houston, H.; Jivraj, T.; Drasar, B. S.; Hill, M. J. *J Clin Invest* 61(4): 953-963; 1978.

The effect of diets containing either 62 or 152 g/day of fat (mainly animal) on the bowel habits, gastointestinal transit time, fecal microflora pattern, and fecal bile acids and fat excretion of six healthy men was observed over a 4-wk period. The only significant change was a higher total fecal bile acid and fatty acid excretion in subjects on the high-fat diet. These results would support a theory linking colonic cancer with increased fecal bile acid excretion due to increased dietary fat intake. (73 refs)

78-5124 **Analysis of Mutagen-Antimutagen Reactions in Food and Food Additives by the Rec-Assay and Reversion-Assay Procedures (Meeting Abstract).** (Eng) Kada, T. (Natl. Inst. Genetics, Misima, Sizuoka-ken, Japan); Sadaie, Y.; Hara, M. *Mutat Res* 53(2): 206-207; 1978. (no refs)

78-5125 **CMOS: Environmental and Human Safety.** (Eng) Singer, E. J. (Res. Center, Lever Brothers Co., Edgewater, NJ); Mones, E.; Rothenstein, A. S.; Weaver, J. M. *Soap/Cosmetics/Chemical Specialties* 54(8): 38-44; 1978.

The results of environmental and biological studies of CMOS (a soluble nonphosphate detergent builder) are reported. CMOS was readily biodegradable, and no accumulation is expected in the food chain. None of the CMOS salts tested showed any potential to induce cancer or mutations or to affect the reproductive performance or development of offspring. It was concluded that this compound will have no adverse environmental or health effects. (6 refs)

78-5126 **The Goitrogenic Effect of 4,4′-Oxydianiline in Rats and Mice.** (Eng) Hayden, D. W. (Dept. Veterinary Pathology, Coll. Veterinary Medicine, Univ. Minnesota, St. Paul, MN, 55108); Wade, G. G.; Handler, A. H. *Vet Pathol* 15(5): 649-662; 1978.

The carcinogenicity of 4,4′-oxydianiline (OD) was studied in Fischer 344 rats and B6C3F$_1$ mice maintained for 13 wk on diets containing 0.03%, 0.06%, 0.1%, or 0.2% of the compound. Stunted growth and morbidity were apparent in animals given 0.06% or more OD, and lethargy was observed in the 0.1% and 0.2% groups. Alopecia, dyspnea, and cyanosis were also seen in rats given the two highest doses. Mortality was observed only among the rats, and it was two times higher among females than in males: 4/10 females in the 0.1% group and 7/10 females in the 0.2% group died. Pathologic findings in the rats included bilateral thyroid enlargement that included the isthmus, presence of clear or red-tinged ascitic fluid, accentuation of the lobular pattern of the liver, atrophy of the male gonads and seminal vesicles, and embedment of the pancreas in gelatinous tissue. Slight to moderate thyroid enlargement was noted in some mice. Microscopic lesions in the thyroid, pituitary, and testes of both species and the prostate, seminal vesicles, kidneys, and bone marrow of rats were related to the chemical and its concentration in the diet. The data showed that OD has a goitrogenic effect and can alter thyroid function to initiate pituitary hyperplasia. (16 refs.)

78-5127 **Biphasic Change of Proton Magnetic Relaxation Times During Azo-Dye Hepatocarcinogenesis.** (Eng) Kodama, M. (Biophysics Div., Natl. Cancer Center Res. Inst., Tsukiji 5-1-1, Chuo-ku, Tokyo 104, Japan); Ohki, T.; Saito, H.; Nagata, C.; Tagashira, Y. *Br J Cancer* 37(2): 233-236; 1978.

The correlation between neoplastic change and change in the proton longitudinal relaxation times (T_1) in the liver, kidney, and blood serum of male Sprague-Dawley rats was studied for periods $\geq$150 days. This is the first report of such studies covering the whole process of azo-dye hepatocarcinogenesis. Rats were fed a diet containing 0.06% 3-methyl-4-dimethylaminoazobenzene for 87 days. The T_1 and water content of liver, kidney, and blood serum were measured. The T_1 of the liver exhibited two maxima, on days 60 and 160. The change of T_1 correlated well with the change in water content, which also showed two maxima on days 60 and 160. The formation of hepatic nodules was observed macroscopically

on day 60. Histological examinations revealed that the first peak of T_1 coincided, not with the disappearance of original hepatocytes, but with the proliferation of renewed hepatocytes. The second peak coincided with the development of hepatomas. Normal hepatic regions adjoining the tumors showed low T_1 values; thus, the change of T_1 accompanying the primary hepatoma was localized. (12 refs)

78-5128 **Multigeneration Reproduction Studies with Carmoisine in Rats.** (Eng) Holmes, P. A. (Illinois Inst. Technology Res. Inst., Chicago, IL); Pritchard, A. B.; Kirschman, J. C. *Toxicology* 10(2): 169-183; 1978.

The effects of carmoisine (CM: a water-soluble red azo dye that is the disodium salt of 2-(4-sulfo-1-naphthylazo)-1-naphthol-4-sulfonic acid) on overall reproductive capacity were studied in three generations of Sprague-Dawley rats. The rats were exposed to 0%, 0.35%, 0.8%, or 2.0% CM in the diet for various time periods up to 1 yr. No significant effect was seen in fertility and copulation indices, birth statistics, offspring viability, or wt of pups. These results indicate a max no-effect level of 2% in the diet. A shorter term study involving the feeding of CM at very high levels (0%, 2%, 4%, 6%, or 8% for 9 wk) was made to establish the highest no-effect level possible. The rats showed normal wt gain with up to 4% CM in the diet. The wt loss observed at 6% and 8% CM may be due to a caloric deficit because of the high percentage of a nonnutritive substance (the CM) in the diet rather than a direct toxic effect of CM itself. These studies indicate that the max no-effect level for CM may be $> 2\%$, since 4% was tolerated without evidence of overt toxicity. (4 refs.)

78-5129 **A One Year Feeding Study with Carmoisine in Rats.** (Eng) Holmes, P. A. (Illinois Inst. Technology Res. Inst., Chicago, IL); Pritchard, A. B.; Kirschman, J. C. *Toxicology* 10(2): 185-193; 1978.

The effects of long-term exposure to carmoisine (CM: a water-soluble red azo dye that is the disodium salt of 2-(4-sulfo-1-naphthylazo)-1-naphthol-4-sulfonic acid) were studied in the F-2b generation of Sprague-Dawley rats fed CM in a multigeneration reproduction study. The F-2b rats were exposed to 0.35%, 0.8%, or 2.0% CM in the diet for 52 wk and then sacrificed. Body wts, hematological values, urinalyses, and relative organ wts were not significantly different from those of controls. No malignant tumors were diagnosed. The incidence of nonneoplastic lesions was the same in both treated and control females. In males receiving 2.0% CM, a significantly higher incidence of minimal bronchitis (6 cases/13 tissues examined), tracheal inflammation (6/13), and lymph node congestion (7/13) was noted. It is suggested that the max no-effect level after 1 yr of CM in the diet is 0.8%, or 400 mg/kg/day. However, since the deleterious effects seen at the 2.0% level were considered minimal, the no-effect level may actually be much higher than 0.8%. (3 refs.)

78-5130 **Hepatic Tumors after Oral Contraceptives (Meeting Abstract).** (Fre) Begue, J. Y. (No affiliation given); Leclere, J.; Bigard, M. A.; Laugros, A.; Gaucher, P.; Rauber, G. *Gastroenterol Clin Biol* 2(5): 558; 1978. (no refs)

78-5131 **Benign Tumors of the Liver and Oral Contraceptives.** (Fre) Letoublon, C. (Service des Urgences Chirurgicales, Clinique Obstetricale et Gynecologique du C.H.U. de Grenoble, Hopital Nord, 38700 La Tronche, France); Champetier, J.; Benbassa, A.; Durand, A.; Laborde, Y.; Pasquier, D. *Lyon Chir* 74(2): 121-124; 1978.

The case reports of two women (aged 36 and 33 yr), each with a hepatic hamartoma, are presented. The women had taken oral contraceptives for 4 and 7 yr, respectively. The histology of one of the tumors, which had been attached to the sigmoid colon, is presented. A review of 172 cases of benign hepatic tumor associated with oral contraceptive use indicated that the risk of developing a benign hepatic tumor is probably small. Hemorrhage with tumor rupture was the most severe complication: it occurred in $>25\%$ of the cases, mostly in adenomas. (15 refs)

78-5132 **Mammary Nodules in Beagle Dogs Administered Investigational Oral Contraceptive Steroids.** (Eng) Giles, R. C. (Dept. Veterinary Pathology, Armed Forces Inst. Pathology, Washington, DC, 20306); Kwapien, R. P.; Geil, R. G.; Casey, H. W. *J Natl Cancer Inst* 60(6): 1351-1364; 1978.

Of 172 beagle dogs given oral contraceptive steroids for 5-7 yr, 114 developed 1,156 nodules in the mammary gland region. Most of these nodules arose 2.5-3.5 yr after initiation of treatment. Approx 16% of the nodules disappeared spontaneously. A total of 925 nodules were present in 99 dogs at the time of death or necropsy. These nodules were classified as benign mammary dysplasias (7.0%), lobular or intraductal hyperplasias (31.4%), simple adenomas (20.8%), complex adenomas (25.4%), benign mixed tumors (5.3%), malignant tumors (3.6%), or nonmammary lesions (6.5%). Histologically, the mammary nodules were representative primarily of the hyperplasias and tumors that occur spontaneously in canine mammary glands. The major exception was the presence of 82 simple adenomas that had basaloid features. Most of the contraceptive-related mammary nodules developed in dogs receiving the combination of progestin and mestranol at 10 or 25 times the proposed human dose. Control dogs and dogs receiving mestranol alone had few mammary nodules. Combinations of anagestone acetate and mestranol and chloroethynyl norgestrel (WY-4355) and mestranol produced large numbers of nodules at 10 and 25 times the proposed human dose; ethynerone plus mestranol produced large numbers of nodules only at 25 times the proposed dose. Ethynerone, when given alone at 25 times the proposed dose, was associated with fewer mammary nodules. Malignant neo-

sms were seen in dogs given 10 and 25 times the proposed man dose of anagestone acetate plus mestranol and 25 es the proposed dose of WY-4355 plus mestranol and ynerone plus mestranol. This study strongly associates tain combinations of progestin and mestranol with mam-ry neoplasia in dogs. (39 refs)

-5133 **Oral-Contraceptive-induced Benign Liver Tumors--The Magnitude of the Problem (Letter to itor).** (Eng) Jick, H. (Boston Collaborative Drug Surveil-ce Program, Boston Univ. Medical Center, Boston, MA); rman, R. *JAMA* 240(9): 828-829; 1978.

e annual number of benign liver tumors induced by oral ntraceptives (OC) in the US estimated made based on (1) ormation obtained between 1970 and 1976 by the Commis-n on Professional and Hospital Activities (covering 40% patients discharged from US hospitals) and (2) information such tumors obtained in a study of 477 US hospitals dur-g 1970-1975. The number was estimated to be roughly 100 d 140/yr, respectively, or one benign tumor for approx ,000 users. (3 refs.)

-5134 **Estrogen Induction of Growth Factors Specific for Hormone-responsive Mammary, Pituitary, d Kidney Tumor Cells.** (Eng) Sirbasku, D. A. (Dept. Bio-emistry and Molecular Biology, Univ. Texas Medical Sch. Houston, P.O. Box 20708, Houston, TX, 77025). *Proc Natl ad Sci USA* 75(8): 3786-3790; 1978.

ie problem of estrogen-promoted tumor cell growth was idied extensively in an attempt to establish the direct mito-nic role of steroid hormones. Permanent cell lines were veloped from three estrogen-responsive rodent tumors: TW9/PL estrogen-, thyroid hormone-, and prolactin-re-onsive rat mammary tumor cells; GH3/C14 estrogen- and yroid hormone-responsive rat pituitary tumor cells; and -301 estrogen-responsive hamster kidney tumor cells. All ree cell lines required estrogens from optimal tumor forma-n in host animals, but they did not respond to estrogens prolactin with increased cell growth rate, as measured by creased cell number, in culture. Extracts of rodent uterus, dney, and liver were found to contain growth-promoting tivity for all three tumor lines. Estrogen treatment in-eased the tissue content of these activities, and the estro-n-induced activities were specific for the estrogen-respon-e cells. The data suggest that estrogen-responsive tumor owth in vivo involves estrogen stimulation of uterus, kid-y, or liver to produce specific growth factors that, in turn, mulate estrogen-responsive tumor cells. (37 refs.)

-5135 **Sex Hormones and Intra-Cranial Gliomata (Meeting Abstract).** (Eng) Hopewell, J. W. (Res. Inst., Churchill Hosp., Oxford, England). *Br J Cancer* 38(1): 171; 1978. (no refs)

78-5136 **Colchicine-like Effect of Diethylstilbestrol (DES) on Mammalian Cells In Vitro.** (Eng) Sawada, M. (Dept. Chemical Pathology, Natl. Inst. Hygienic Sciences, 1-18-1 Kamiyoga, Setagaya-ku, Tokyo 158, Japan); Ishidate, M. *Mutat Res* 57(2): 175-182; 1978.

The cytological effects of diethylstilbestrol (DES) on mammalian cells in culture were examined in the following cell lines: CHT, derived from the thymus of a young male Chinese hamster; DL, derived from a Japanese Donryu rat liver; EDEN-1/TC, derived from a rat erythroblastic leukemia; and HeLa-S3. Metaphase arrest was induced 3 hr after treatment with 15 μg/ml DES, and polyploid or polynucleated cells were prominent >24 hr after treatment. The arrest was reversible when the agent was removed from the medium. Tetraploid karyotypes induced by DES in CHT cells consisted of double sets of diploid chromosomes except for one marker chromosome, which may have been formed by fusion or translocation of two No. 4 chromosomes. However, this marker may not be DES-specific, as it was not detected in other lines after DES treatment. By clonal selection, several hypotetraploid sublines were successfully isolated from a CHT cell population after it was treated with 15 μg/ml DES for 48 hr. These studies demonstrate that DES has a direct effect on cell mitosis in vitro, probably on the formation of the spindle apparatus, similar to the effect induced by colchicine. (21 refs)

78-5137 **Cytogenetic Studies with Diethyl Stilboestrol.** (Eng) Bishun, N. P. (Tissue Culture and Cytogenetics Unit, Marie Curie Memorial Foundation, The Chart, Oxted, Surrey, England); Eddie, H.; Williams, D. C. *Clin Oncol* 4(2): 159-165; 1978.

Normal human peripheral blood WBC, two human carcinoma cell lines, and one established rat cancer cell line were exposed in culture to diethylstilbestrol at levels of 20, 15, 10, or 5 μg/ml and examined for chromosome aberrations. No significant chromosome damage was noted at any of the concentrations used. The discrepancy between these findings and previous results is discussed. (6 refs.)

78-5138 **Oxidative Metabolites of Diethylstilbestrol in the Fetal, Neonatal and Adult Mouse.** (Eng) Metzler, M. (Inst. Toxicology, Univ. Wurzburg, D-8700 Wurzburg, W. Germany); McLachlan, J. A. *Biochem Pharmacol* 27(7): 1087-1094; 1978.

Urinary metabolites of ^{14}C-labeled diethylstilbestrol (DES) in adult female mice were identified by radio gas chromatogra-

phy and gas chromatography-mass spectrometry as β-dienestrol and the ω-hydroxy derivatives of DES, ψ-DES, and dienestrol. β-Dienestrol did not appear to be formed through a DES epoxide. It is suggested that DES might be oxidized to a p-quinone, which could easily be tautomerized to β-dienestrol. Most of the metabolites found in adult mice were also detected by mass fragmentography in the whole-body homogenates obtained from 1-, 4- and 8-day-old mice, indicating that oxidative metabolism of DES is operative in neonatal mice. Extensive conjugation of DES and its metabolites to glucuronic acid was found in adult and neonatal mice. Part of the administered radioactivity was unextractable from tissue macromolecules in neonatal mice. The biotransformation of DES and the binding of its metabolites might be associated with its teratogenic and carcinogenic potential for neonatal and fetal mice. (34 refs)

78-5139 **Diethylstilbestrol Binding to Estrogen Receptor in Mammary Tissue and Uteri of C3H/HeJ Mice.** (Eng) Okey, A. B. (Dept. Biology, Univ. Windsor, Windsor, Ontario, Canada N9B 3P4); Bondy, G. P. *J Natl Cancer Inst* 61(3): 719-724; 1978.

Diethylstilbestrol (DES) binding to components in mammary cytosol from C3H/HeJ mice was assessed directly (with ^{3}H-DES) and indirectly [by competition between DES and ^{3}H-17β-estradiol (E_2)]. On sucrose density gradients, the qualitative properties of cytosol estrogen receptor were similar whether ^{3}H-DES was used as the ligand or whether the receptor was labeled with ^{3}H-E_2. Binding of either ^{3}H-DES or ^{3}H-E_2 was extinguished by incubation in the presence of a 100-fold excess of unlabeled DES or E_2. ^{3}H-DES also sedimented with a component in the 4S-5S region; this component bound much larger quantities of ^{3}H-DES than ^{3}H-E_2 and was not eliminated by incubation with a 100-fold excess of unlabeled estrogen. Both ^{3}H-E_2- and ^{3}H-DES-labeled receptors dissociated to a 4S-5S form when centrifuged on gradients containing 0.4 M KCl. DES also induced receptor transformation and nuclear uptake, as evidenced by recovery of a 5S-region receptor from mammary nuclei of mice given injections in vivo with ^{3}H-DES. Dextran-coated charcoal assays/Scatchard plot analyses with ^{3}H-DES indicated a DES-receptor interaction with a dissociation constant of 2.6 x 10^{-10} M compared with 6.3 x 10^{-11} M for ^{3}H-E_2. By competition studies, the apparent affinity of receptor for DES was essentially the same as that for E_2. The apparent concentration of high-affinity binding sites in mammary cytosol was higher for ^{3}H-DES than for ^{3}H-E_2; this probably was due to ^{3}H-DES binding to nonreceptor proteins, possibly serum albumin. Overall, intracellular (receptor) binding of DES did not appear to be fundamentally different from binding of natural estrogens. (24 refs.)

78-5140 **Acute Myeloblastic Leukemia Following Chlorambucil Treatment. Two New Cases.** (Fre) Witz, F. (Clinique Medical A, C.H.U., Nancy-Brabois, F 54500 Vandoeuvre, France); Lederlin, P.; Aymard, J. P.; Thibaut, G.; Guerci, O. *Nouv Presse Med* 7(27): 2392; 1978.

Two women, aged 47 and 52 yr, developed acute myeloblastic leukemia following long-term treatment with chlorambucil for multiple sclerosis. Each patient received 6 mg/day for a total dose of 13.3 g in 75 mo and 9.9 g in 55 mo, respectively. Both women died. (3 refs.)

78-5141 **Comparative Study of Mutagenic Activity of a Series of Hypotensive Drugs in Mice.** (Rus) Zolotareva, G. N. (Res. Inst. Biological Trials of Chemical Compounds, Moscow, USSR); Akaeva, E. A.; Iskhakova, E. N.; Oblapenko, N. G.; Kotelianskaia, A. E.; Epshtein, S. I. *Khim Farm Zh* 12(3): 19-22; 1978.

The potential mutagenic activity of a series of hypotensive drugs [reserpine, its commercial forms raucedil and raunatine, and clopheline, or 2.2,6-dichlorophenylamino)-2-imidazoline hydrochloride] was tested in CBA x C57BL/6 mice. The drugs were given ip and po, at levels ranging from $0.5/LD_{50}$ to therapeutic dosages. Mutagenicity was measured by the incidence of chromosome aberrations in bone marrow cells and by the induction of dominant lethals in germ cells. Raucedil at (10 and 5 mg/kg) and raunatine at (15 and 10 mg/kg) increased the incidence of single fragments, but therapeutic doses of these drugs lacked mutagenic activity. Clopheline at all doses tested showed no mutagenic activity. Exposure of male mice to reserpine decreased the number of pregnant females and increased the preimplantation death of the zygotes. (5 refs)

78-5142 **Thyroid Tumours in Rats and Hepatomas in Mice after Griseofulvin Treatment.** (Eng) Rustia, M. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, Omaha, NB, 68105); Shubik, P. *Br J Cancer* 38(2): 237-249; 1978.

The carcinogenicity of the antibiotic, griseofulvin, was studied in Swiss mice, MRC-Wistar rats, and Syrian hamsters. Three groups of mice and rats were given the drug in a powdered diet in alternating 5-wk periods for life, at dose levels of 3.0%, 1.5%, and 0.3% (mice) and 2.0%, 1.0%, and 0.2% (rats). A fourth group of mice received continuous daily treatment for life with 0.1% griseofulvin, and three groups of hamsters were similarly treated at levels of 3.0%, 1.5%, and 0.3%. In mice, the two highest doses produced a significant incidence of hepatic tumors in both males and females. At the 3.0% level, females had a higher percentage of hepatomas than males (87% vs 83.3%); at the 1.5% level, males had a higher percentage than females (68% vs 53.6%). Histologically, the liver tumors were either well-differentiated and solid, with a structure similar to that of normal liver; less-differentiated and trabecular; or (occasionally) glandular, in

hich case the liver structure was completely obliterated. ontrary to previous findings, statistically significant rates ≤ 0.001 and/or P ≤ 0.02) of thyroid tumors were record- in male rats at all dose levels and in females at the two gher levels. A classic dose-response relationship was ob- rved. Histologically, the thyroid tumors were predominant- adenomas, consisting of follicles (macro- or microfollicular pes) and/or papillary-cystic structures. In hamsters, no oplasms developed in response to treatment at any level. l refs)

-5143 Accelerated Growth of Mammary Tumor Cells in Normal and Athymic Mice after Treatment Vitro with Dexamethasone. (Eng) Gillette, R. W. (Cancer enter Hawaii, Honolulu, HI, 96822); Wunderlich, D. A. *ancer Res* 38(10): 3146-3149; 1978.

he tumorigenicity of dexamethasone (DM)-treated C3HMT ouse mammary adenocarcinoma cells was compared with at of untreated C3HMT cells. Cultures of tumor cells were eated with 0.1 μg/ml DM and harvested after 4 days of eroid treatment. DM increased RNA-directed DNA olymerase activity in the cultures, which indicated increased urine mammary tumor virus expression. Both treated and ntreated cells induced tumors in 20/20 C3H mice inoculat- l sc with 10^6 cells. At doses of 10^5, 10^4, and 10^3 cells however, mors were noted in 19/19, 14/20, and 8/20 mice receiving M-treated cells, respectively, compared with 15/20, 2/20, nd 0/20 in mice receiving the untreated cells. Further stu- es suggested that the DM treatment did not measurably ange the immunogenicity of the C3HMT cells. Upon injec- on of 10^5 treated or untreated cells into athymic nude mice, l animals developed tumors, but the DM-treated tumors rogressed more rapidly. Thus, immunostimulation by T lls was not a factor in the accelerated growth of the M-induced tumor cells. DM treatment (1 mg) of the host the time of tumor cell inoculation did not influence tumor owth, but thrice weekly injections of 1 mg DM for 3 wk ter tumor inoculation had a negative effect on C3HMT pro- ession. The possibility of DM immunostimulation of other nds of lymphoid cells is discussed. (12 refs.)

8-5144 Oncogenic Transformation In Vitro by the Hypoxic Cell Sensitizer Misonidazole. (Eng) Iiller, R. C. (Radiological Res. Lab., Coll. Physicians and urgeons Columbia Univ., New York, NY, 10032); Hall, E. *Br J Cancer* 38(3): 411-417; 1978.

he effect of the hypoxic cell sensitizer Misonidazole (MIS; o-07-0582) on aerated C3H/10T1/2 cells was determined. ultured cells were exposed to varying doses of radiation nd/or to 0.4-8.0 mM MIS for 3 days or 0.5-2.0 mM MIS r 6 days. Doses as low as 0.4 mM resulted in a significant ansformation rate. This rate clearly increased with dose. owever, the period during which MIS was in contact with the cells had little influence on the number of cells transformed. A concentration of 0.4 mM for 3 or 6 days resulted in a transformation rate comparable to that observed following an x-ray dose of 1 Gray. A concentration of 6.0 mM was equivalent to 4 Gray. When cells were exposed to 1 mM MIS for 3 days and, 24 hr after the start of MIS exposure, to 1, 2, or 4 Gray of x-rays, there was a significant increase in the frequency of transformation over that seen with either the drug or the radiation alone. It is not known whether the action between the two agents was additive or synergistic. (18 refs.)

78-5145 Caffeine Inhibition of Prereplication Repair of Mitomycin C-induced DNA Damage in Human Peripheral Lymphocytes. (Eng) Ishii, Y. (Dept. Fundamental Radiology, Faculty Medicine, Osaka Univ., Kita-ku, Osaka 530, Japan); Bender, M. A. *Mutat Res* 51(3): 419-425; 1978.

The effect of caffeine (0-300 μg/ml) on the prereplication repair of mitomycin C (MMC)-induced DNA damage in human peripheral lymphocytes was studied. Caffeine alone induced some sister chromatid exchanges (SCEs) and also interacted synergistically to produce large increases in the yields of MMC-induced SCE's. This enhancement decreased when the MMC-treated cells were held in medium before phytohemagglutinin (PHA) stimulation or when caffeine was added to the cultures some time after PHA stimulation but prior to DNA synthesis. The data confirm the existence of a caffeine-sensitive prereplicational DNA repair mechanism in human peripheral lymphocytes. It appears that this repair system becomes saturated and is only capable of repairing a fraction of those MMC-induced DNA lesions capable of inducing SCE's. (45 refs.)

78-5146 Cancers among Users of Preparations Containing Vitamin A. A Case-Control Investigation. (Eng) Smith, P. G. (DHSS Cancer Epidemiology and Clinical Trials Unit, Univ. Oxford, 9 Keble Road, Oxford, England); Jick, H. *Cancer* 42(2): 808-811; 1978.

The regular use of vitamin A preparations was determined among 800 newly diagnosed cancer patients and 3,433 patients with certain nonmalignant conditions. The age range of both groups was 20-75 yr. Regular usage was defined as at least once a week for the 3-mo period or more prior to hospital admission. Overall, there was no convincing evidence that regular consumption of such preparations protected against the development of cancer (risk ratio 0.85). However, there was a suggestion of a negative association among men (risk ratio 0.54) but not among women (risk ratio 1.11). The negative association among men did not increase with the period that the preparations had been regularly taken and was not greater for squamous cell tumors. There is experimental evidence from animal experiments and in vitro labora-

tory investigations indicating that vitamin A deficiency predisposes to squamous metaplasia and that vitamin A protects against the development of some chemically induced neoplasms, particularly squamous carcinomas. (8 refs.)

78-5147 **Aplasia and Leukaemia Following Chloroquine Therapy.** (Eng) Nagaratnam, N. (General Hosp., Colombo, Sri Lanka); Chetiyawardana, A. D.; Rajiyah, S. *Postgrad Med J* 54(628): 108-112; 1978.

Case reports are presented for three patients who developed aplastic anemia following chloroquine (CQ) therapy. A 69-yr-old man, who subsequently developed acute myeloblastic leukemia, had taken large doses for several months for the treatment of discoid lupus erythematosus. A 29-yr-old woman had received CQ for malaria on several occasions and had been on prophylactic CQ for several months. In a 22-yr-old man, anemia with neutropenia occurred after a 3-wk course of CQ for malaria. Although parallels can be drawn with chloramphenicol-induced blood dyscrasias, the relationship between CQ and bone marrow injury is unclear. (12 refs)

78-5148 **Carcinogenic and Other Adverse Effects of Procarbazine in Nonhuman Primates.** (Eng) Sieber, S. M. (Lab. Chemical Pharmacology, NCI, NIH, Building 37, Room 5A13, Bethesda, MD, 20014); Correa, P.; Dalgard, D. W.; Adamson, R. H. *Cancer Res* 38(7): 2125-2134; 1978.

The carcinogenic and toxic effects of procarbazine (PRO) were investigated in 55 monkeys who received the drug sc, po, or ip for periods of up to 12 yr. Thirteen monkeys are alive and without evidence of tumor. Among the 42 animals that were necropsied, 11 have had malignant neoplasms. The malignancies included 6 cases of acute leukemia (5 myelogenous and 1 undifferentiated), 2 of osteogenic sarcomas, 2 hemangiosarcomas, and 1 lymphocytic lymphoma. In contrast, only 2/211 control and breeder monkeys maintained during the same time period developed malignant tumors. The av total dose of PRO received by the monkeys developing cancers was 36.0 g (range, 2.69-101.65 g), and the av duration of PRO treatment was 75 mo. Two of the 11 monkeys with malignant neoplasms received PRO by ip injections, 7 were given the drug both sc and po, and 2 were treated both ip and po. The toxic effects of PRO included vomiting, myelosuppression, and testicular atrophy, with complete aplasia of the germinal epithelium. (51 refs)

78-5149 **Induction of Sister Chromatid Exchanges In Vivo in Bone Marrow Cells of AKR Mice.** (Fre) Renault, G. (Institut de Recherches scientifiques sur le Cancer [C.N.R.S.], B.P. no. 8, 94800 Villejuif, France); Pot-Deprun, J.; Chouroulinkov, I. *C R Acad Sci [D] (Paris)* 286(11): 887-890; 1978.

Four drugs known for their mutagenic activity were tested in vivo in 3-to 5-mo-old AKR mice for their ability to induce sister chromatid exchanges (SCE). Mice were treated with 5-bromodeoxyuridine for 7 days (40 mg/kg, ip), the test drug was given ip on day 9, colchicine (0.05 mg ip) was injected on day 18, and mice were killed on day 21. SCE were counted in samples of bone marrow obtained from the femurs. In order of decreasing activity, the drugs tested were cyclophosphamide (5-25 mg/kg), procarbazine (25-200 mg/kg), methylmethane sulfonate (25-100 mg/kg), and diethylnitrosamine (10-100 mg/kg). It is concluded that induction of SCE in vivo is an objective measure of the action of chemical agents on the animal. (8 refs)

78-5150 **Potentially Carcinogenic Analogues of the Carcinogen Hexamethylphosphoramide: Evaluation In Vitro.** (Eng) Ashby, J. (Central Toxicology Lab., Imperial Chemical Industries Ltd., Alderley Park, Macclesfield, Cheshire, England); Styles, J. A.; Paton, D. *Br J Cancer* 38(3): 418-427; 1978.

Several analogs of hexamethylphosphoramide were assayed for carcinogenicity using baby hamster kidney cells (BHK 21/C13) and the cell transformation assay of Styles under two metabolic activation conditions: an S-9 microsomal mix at a standard ratio of S-9 fraction to cofactors (1:9 10 μ/tube) or the mix at a modified ratio (1:1; 50 μl). Each experiment was repeated twice. Hexamethylphosphoramide, hexamethylphosphorus triamide, hexamethylphosphorothioic triamide, tripiperidinophosphine oxide, phosphorothioic trimorpholide, and diethoxymorpholinophosphine oxide gave positve responses in this assay. Different transformation frequencies were obtained with the two S-9 mixes, suggesting that a small but widely separated range of S-9 mixes be used in experimental situations in which an initially derived negative response is not compatible with what is already known about, or expected from, a chemical or class of chemicals. It appears that the broad structural requirements for carcinogenicity observed for nitrosamine carcinogens also apply to phosphoramide carcinogens. (18 refs.)

78-5151 **Acute Myelogenous Leukemia Following Immunosuppressive Therapy for Rheumatoid Arthritis.** (Eng) Kapadia, S. B. (Dept. Pathology, Presbyterian-Univ. Hosp., Pittsburgh, PA, 15213); Kaplan, S. S. *Am J Clin Pathol* 70(2): 301-302; 1978.

The development of acute myelogenous leukemia in a 51-yr-old woman following long-term cyclophosphamide therapy for rheumatoid arthritis is reported. During her 4-yr history of cyclophosphamide ingestion, an av daily dose of 25 mg had been administered. The development of pancytopenia resulted in a discontinuation of the drug; however, 4 mo later the pancytopenia had progressed to acute myelogenous leukemia. Cytogenetic study of the marrow cells re-

ealed a missing B-group chromosome in all 20 cells studied nd one to three extra C-group chromosomes in 12/20 cells. hese findings suggest a possible leukemogenic role of cyclo- hosphamide in this case; caution should be exercised in reating nonfatal diseases with antitumor drugs. (19 refs.)

8-5152 **Use of Human-Liver Microsomes from Kidney-Transplant Donors for the Induction of hromatid Aberrations and Sister-Chromatid Exchanges by leans of Pre-carcinogens in Chinese Hamster Cells In Vi- o.** (Eng) Thust, R. (Res. Group Preventive Oncology, Inst. athology, Medical Acad. Erfurt, Nordhauser Strasse 74,)DR-50 Erfurt, E. Germany); Warzok, R.; Grund, E.; Men- el, J. *Mutat Res* 51(3): 397-402; 1978.

he induction of chromatid aberrations and sister chromatid xchanges (SCE's) in Chinese hamster fibroblasts by cyclo- hosphamide (CP) and dimethylnitrosamine (DMN) meta- olized by human liver microsomes in combination with an ADPH-generating system was studied. The liver mi- rosomes were obtained from two kidney transplant donors. he liver microsomes from one subject, who also suffered om Gaucher's disease, activated CP and DMN to induce hromatid aberrations and a slight increase in SCE's. The icrosomes from this subject metabolized DMN at the same vel as uninduced rat liver microsomes. The microsomes om the second subject failed to activate CP, but they did ctivate DMN, although to a somewhat lesser extent than t-liver microsomes or the microsomes from the first subject. ased on absolute concentration, DMN showed slight SCE duction compared with CP. The use of tissues from renal ansplant donors can provide a practicable means for study- g the metabolism of carcinogens and for detecting active etabolites by means of genetic and cytogenetic assays. (16 fs.)

8-5153 **Acute Leukemia Following Immunosuppressive Therapy for Disseminated Sclerosis and for ehcet's Syndrome.** (Fre) Mougeot-Martin, M. (Clinique ledicale "A", Hopital Saint-Antoine, 184, rue du Faubourg aint-Antoine, F 75571 Paris Cedex 12, France); Krulik, M.; arousseau, J. L.; Audebert, A. A.; Chaouat, Y.; Debray, J. *nn Med Interne (Paris)* 129(3): 175-180; 1978.

he development of acute myelocytic leukemia (AML) in vo patients treated with immunosuppressive drugs is report- l, and the literature is reviewed. Evidence of AML was not- l in the first patient, a 52-yr-old woman, after 49 mo of eatment with cyclophosphamide (100 mg/day, then 50 g/day: total dose 81 g) for Behcet's syndrome. The second atient, a 47-yr-old woman, developed anemia and leukemia ith a high proportion of myeloblasts in the bone marrow fter 2 yr of therapy with chlorambucil (6 mg/day) for multi- le sclerosis. The latent period between the end of therapy nd the appearance of AML was 2 yr. A total of 33 cases of cute leukemia following immunosuppressive therapy with chlorambucil, cyclophosphamide, azathioprine, melphalan, methotrexate, and busulphan are summarized. There were 16 men and 17 women aged 21-71 yr (av age 50.8 yr). The patients were treated for a variety of diseases, but rheumatoid arthritis was the most frequent (13/33). Except for two patients treated 4.5 and 6 mo, respectively, duration of treatment was 12 mo or more (av 37.9 mo). The time between the end of treatment and the leukemia was 14.3 mo on the av. There was only one lymphocytic leukemia; three were undifferentiated, and the rest were myelocytic. Possible mechanisms of action of leukemia induction by immunosuppressive therapy are discussed. (41 refs)

78-5154 **Sister Chromatid Exchanges Induced by Cyclophosphamide in V79 Cells Cultured in Diffusion Chambers in Mice.** (Eng) Furukawa, M. (Dept. Experimental Biology, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263); Huang, C. C. *Mutat Res* 57(2): 233-239; 1978.

Line V79 Chinese hamster cells, cultured in diffusion chambers (DC) and implanted into mice, were tested as a potential assay system for mutagenicity. An exponential growth was observed from days 2-4 after implantation. Max growth was reached on day 6. After that, cell growth and viable cell counts decreased. Three days after implantation of DC with V79 cells, the hosts received six hourly injections of 0.2 ml 5-bromodeoxyuridine (BUdR) soln at concentrations of 0.125 to 1.0 x 10^{-2} M. DC were removed and analyzed for chromosome and sister chromatid exchanges (SCE) 24 hr after the first BUdR injection. The frequency of metaphases with differentially stained chromatids and with aberrations and the number of SCE per cell increased with BUdR dose. The frequency of metaphases with differentially stained chromatids was also positively correlated with the duration of BUdR exposure or the number of hourly injections of BUdR. The effects of cyclophosphamide (CY) were also studied. Injections of 2.5, 5, 10, and 15 μg/g into hosts carrying V79 cells in DC increased in the number of SCE per cell in a linear manner. There was no increase of chromosome aberrations compared with controls. This study indicates that V79 cells cultured in DC in mice may prove to be a sensitive test system for screening potential mutagens or carcinogens, especially those that require metabolic activation. (26 refs)

78-5155 **Cytogenetics in Short-Term Tests (Meeting Abstract).** (Eng) Hughes, L. O. (Pharmaceuticals Div., Imperial Chemical Industries, Ltd., Macclesfield, Cheshire, England); Topham, J. C. *Mutat Res* 53(2): 203; 1978. (no refs)

78-5156 **The Nucleus Anomaly Test as a Sensitive Method of Detecting Mutagenic Effects on Somatic Cells (Meeting Abstract).** (Eng) Langauer, M. (Res. Dept.,

Pharmaceuticals Div., CIBA-GEIGY Ltd., Basel, Switzerland); Muller, D. *Mutat Res* 53(2): 216-217; 1978. (2 refs)

78-5157 **Mutagenic Effects of Different Mutagens on Human Chromosomes In Vitro and In Vivo as Detected by Conventional and 'Harlequin' Methods (Meeting Abstract).** (Eng) Kucerova, M. (Pediatric Dept., Postgraduate Medical Inst., Prague, Czechoslovakia); Polivkova, Z. *Mutat Res* 53(2): 215; 1978. (no refs)

78-5158 **Comparative Mutagenicity of Alkylsulfate and Alkanesulfonate Derivatives in Chinese Hamster Ovary Cells.** (Eng) Couch, D. B. (Chemical Industry Inst. Toxicology, Research Triangle Park, NC, 27709); Forbes, N. L.; Hsie, A. W. *Mutat Res* 57(2): 217-224; 1978.

The mutagenicity and cytotoxicity of several alkyl sulfates and alkane sulfonates were quantitated using the Chinese hamster ovary/hypoxanthine-guanine phosphoribosyltransferase system. Dose-response relationships were examined for two alkyl sulfates, dimethyl sulfate (DMS) and diethyl sulfate (DES), and three alkyl alkanesulfonates, methyl methanesulfonate (MMS) ethyl methanesulfonate (EMS), and isopropyl methanesulfonate (iPMS). Cytotoxicity decreased with the size of the alkyl group. DMS was more toxic than DES, and MMS was more toxic than EMS and iPMS. All agents gave a linear dose response of mutation induction: DMS was more mutagenic than DES and MMS was more mutagenic than EMS and iPMS, based on mutants induced per unit of mutagen concentration. When comparisons were made at 10% survival, however, the following relative mutagenic potency was observed; DES > DMS; EMS > MMS > iPMS. It does not appear that mutagenic potency, as determined in this study, is clearly associated with S(n)1 (unimolecular nucleophilic substitution) reactivity. iPMS has been reported to have the greatest S(n)1 reactivity, but it was less mutagenic than DES or EMS. (21 refs)

78-5159 **Promotion of Azoxymethane-induced Colonic Neoplasia by Resection of the Proximal Small Bowel.** (Eng) Williamson, R. C. (Dept. Surgery, Bristol Royal Infirmary, Bristol, England); Bauer, F. L.; Oscarson, J. E.; Ross, J. S.; Malt, R. A. *Cancer Res* 38(10): 3212-3217; 1978.

Potential enhancement of intestinal neoplasia by compensatory mucosal hyperplasia was tested in male Fischer rats subjected to 50% proximal small bowel resection (PSBR) 10 days after the last of 16 weekly injections of 10 mg azoxymethane (AZM). AZM alone increased the jejunal contents of RNA and DNA each by 26% at 17-18 wk before there was macroscopic evidence of neoplasia. Three months after PSBR alone, ileal hyperplasia was characterized by increased amounts of RNA (42%-76%) and DNA (68%-95%), taller villi, deeper crypts, and luminal dilation; however, the colon showed only patchy hyperplasia. When the combined effects of AZM and PSBR were observed 26-30 wk after the first injection, rats with PSBR had an increased number of colonic tumors/animal (2.9 vs 1.6 for controls). Despite the intense ileal hyperplasia produced by PSBR, ileal neoplasia did not occur. Thus, enhanced colonic carcinogenesis was only observed following sequential exposure of the mucosa to the carcinogen and the promoting factors. (43 refs.)

78-5160 **A Study of the Mutagenicity of Anesthetics and Their Metabolites.** (Eng) Waskell, L. (Dept. Biochemistry, Univ. California, Berkeley, CA, 94720). *Mutat Res* 57(2): 141-153; 1978.

The commonly used volatile anesthetics, several of their metabolites, and drugs frequently used by the anesthesiologist were screened for mutagenicity in the Ames *Salmonella typhimurium*/rat liver microsomal assay system. Chloral hydrate was weakly mutagenic. Other compounds tested, including halothane (1,1,1-trifluoro-2-bromo-2-chloroethane), isoflurane (1-chloro-2,2,2-trifluoroethyldifluoromethyl ether), methoxyflurane (2,2-dichloro-1,1-difluoroethyl methyl ether), diazepam (7-chloro-1,3-dihydro-1,1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one), and chlordiazepoxide (7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine) were not mutagenic. Non volatile compounds were tested for their ability to inhibit growth of bacterial strains with decreased capacity to repair damaged DNA. None of the compounds tested inhibited the growth of DNA repair-deficient strains relative to a strain with normal DNA repair. Halothane and trilene (1,1,2-trichloroethylene) were tested for direct interaction with DNA with negative results. These results support the hypothesis that the inhalation anesthetics, which are chemically stable molecules of low toxicity, are unlikely to react covalently directly with DNA. (49 refs)

78-5161 **Metabolism of Methylated Analogs of Aldrin and Dieldrin by Liver Preparations from Male and Female Rat.** (Eng) Hassall, K. A. (Dept. Physiology and Biochemistry, Univ. Reading, Reading, England); Dionyssiou-Asteriou, A.; Manning, D. *Pestic Biochem Physiol* 8(3): 287-301; 1978.

Aldrin and dieldrin analogs whose molecules lack a methylene bridge but have two methyl groups attached to olefinic or oxirane ring carbon atoms were synthesized, and their metabolism was studied using NADPH-supplemented 12,000 g x 30-min supernates of Wistar and CD strain rat livers. The dimethylated olefin was not metabolized to its epoxide but was converted by rat liver supernates of both sexes to a labile hydroxylated metabolite. Exogenous NADPH increased the rate at which the olefin was metabolized, but concentrations of NADPH that increased the yield of the labile metabolite

hen added to female rat liver preparations decreased the eld when added to those of males. This metabolite had a ass spectrum that was consistent with its being a hydrox- ethyl derivative. The dimethylated epoxide was metabol- d more slowly than the olefin, and a notable sex difference the route of metabolism was evident. With supernate from e livers of female rats, the only metabolite detected by s-liquid chromatography had a mass spectrum consistent th its being a ring-hydroxylated epoxide. Male rat liver pernate formed small quantities of the same compound, but e major metabolite had a mass spectrum indicative of a droxymethyl epoxide. No hydrolysis of the oxirane ring of e epoxide was detected. (17 refs)

-5162 **Study of the Mutagenic Potential of Captan by the Heritable Translocation Test in Mice eeting Abstract).** (Eng) Jorgenson, T. A. (Stanford Res. t., Menlo Park, CA); Rushbrook, C. J.; Newell, G. W.; aters, M. *Mutat Res* 53(2): 206; 1978. (no refs)

-5163 **Effect of Fungicide Folpet on Growth and Chromosomes of Human Lymphoid Cell Lines.** ng) Sirianni, S. R. (Dept. Experimental Biology, Roswell rk Memorial Inst., Buffalo, NY, 14263); Huang, C. C. *Can Genet Cytol* 20(2): 193-197; 1978.

e cytotoxic and cytogenetic effects of Folpet (N-tri- oromethylthiophthalimide; a fungicide used in paints) on rmal (Jeff) and Burkitt (Raji) human lymphoid cell lines re determined. Jeff cells were continuously treated with lpet concentrations of 0.5, 1, 2, and 4 μg/ml media and Raji cells were pulse-treated for 15 min with 2.5, 5, 10, d 15 μg/ml. Various times after treatment, cell viability unts and chromosome analyses were made. Severe cell wth inhibition and an increase in chromosome aberrations re observed in both cell lines. Two types of chromosome errations were induced. Type-B aberrations appeared in tures treated with lower doses, and they were character- d by chromosome or chromatid gaps and breaks; dicen- cs and exchanges were also noted infrequently. In the later ges of the experiment, the cell growth rate and number of errations returned to control levels. Type-B chromosome errations appeared in early samples of cultures treated with her doses of the compound. The aberrations included romosome stickiness, despiralization, and pulverization. e cultures died off within 2 days. Pulse treatment of Jeff tures with the same doses used to treat Raji cells indicated t the former were more sensitive to Folpet than the latter. sed on the clastogenic effect of Folpet in this experiment d the close correlation between clastogens and mutagens, an be inferred that the compound is mutagenic. The envi- mental risk of Folpet as a paint additive needs further dy. (13 refs.)

78-5164 **Determination of Carcinogenicity of O,O-Dimethyl(1-hydroxy-2,2,2-trichloroethyl)-phosphonate (Trichlorfon) in Mice by Oral, Intraperitoneal, and Dermal Application.** (Ger) Teichmann, B. (Zentralinstitut fur Krebsforschung, Akademie der Wissenschaften der DDR, Lindenberger Weg 80, DDR-1115 Berlin-Buch, E. Germany); Hauschild, F. *Arch Geschwulstforsch* 48(4): 301-307; 1978.

The carcinogenicity of O,O-dimethyl(1-hydroxy-2,2,2-trichloroethyl)phosphonate (Trichlorfon; TCP) was investigated in male and female AB/Jena mice. The mice received TCP by po (esophageal-gastric intubation), ip, or dermal administration. In po experiments, male mice received a max of 157.5 mg and females 154 mg over 73 wk. With ip administration, males received a max of 160.8 mg and females 149.7 mg over 73 wk. With dermal application, both sexes received a max of 375 mg TCP over 75 wk. The experiment was terminated at 80 wk. There was no statistically significant difference between the total tumor incidence in TCP-treated animals and controls. In addition, no significant difference in tumor incidence or type was observed among the mice receiving TCP by the different routes. (9 refs.)

78-5165 **Effects of Feeding Lindane to Dogs for Periods of up to 2 Years.** (Eng) Rivett, K. F. (Huntingdon Res. Centre, Huntingdon, England). *Toxicology* 9(3): 273-289; 1978.

The effect of chronic exposure to lindane on dogs were studied by feeding the pesticide to male and female beagles at levels of 25, 50, or 100 ppm for 104 wk or 200 ppm for 32 wk. In a preliminary study in which the same levels were administered for 7 wk, the only changes were decreases in body wt at 100 and 200 ppm and increased liver wt at 200 ppm. In animals given 100 ppm lindane for 104 wk, the only change in the electroencephalogram was a superimposition of slightly irregular slow waves on the normal sleep pattern in two animals. Body wt gain, appetite, urinalysis, ophthalmological and hematological parameters, and organ wt were unaffected. The only biochemical change was a significant elevation in serum alkaline phosphatase (SAP) levels in this group; the livers in this group were also unusually dark. In the 200-ppm group, high-voltage slow-wave activity, which was possibly indicative of a nonspecific neuronal irritation, was observed. SAP levels were also elevated in this group, and the livers were dark, friable, and slightly enlarged. The negative findings in the 25- and 50-ppm groups are consistent with a "no-effect level" of 1.25 mg/kg in dogs that is comparable with that in rats and consistent with the acceptable daily intake of 0.0125 mg/kg proposed for humans. (23 refs)

78-5166 **Children Absorb Tris-BP Flame Retardant from Sleepwear: Urine Contains the Mutagenic Metabolite, 2,3-Dibromopropanol.** (Eng) Blum, A. (Dept. Bi-

ochemistry, Univ. California, Berkeley, CA, 94720); Gold, M. D.; Ames, B. N.; Kenyon, C.; Jones, F. R.; Hett, E. A.; Dougherty, R. C.; Horning, E. C.; Dzidic, I.; Carroll, D. I.; Stillwell, R. N.; Thenot, J. P. *Science* 201(4360): 1020-1023; 1978.

Urine samples from children who were wearing or who had worn sleepwear treated with the flame retardant tris(2,3-dibromopropyl)phosphate (tris-BP) were examined for 2,3-dibromopropanol (DBP), a mutagenic metabolite of tris-BP. Tris-BP is also a mutagen and it causes sterility and cancer in animals. Preliminary studies were made of morning urine samples from a 7-yr-old girl who wore repeatedly washed sleepwear that may have been treated with tris-BP on days 1 and 2 and 8-12 and new tris-BP-treated pajamas on days 3-7. On days 1 and 2, her urine contained 0.4 nanogram (ng)/ml DBP; considerably more DBP (up to 29 ng/ml on day 4) was found in her urine both during and after the wearing of the new pajamas. Urine samples were collected from 10 other children and 1 adult about 5 mo after the sale of new tris-BP-treated pajamas was banned. No DBP was found in the urine of the one child and one adult who had never worn flame-retardant sleepwear. Eight children were wearing well-washed tris-BP-treated sleepwear: seven had urinary DBP levels of approx 0.5 ng/ml and one child had a level of 5 ng/ml. A trace of DBP was found in the urine of one child who reportedly stopped wearing tris-BP-treated sleepwear 6 mo previously. It was estimated that the amount of tris-BP absorbed could be as much as 15 times as high as the amount of DBP found in urine. Absorption of tris-BP from old treated sleepware could pose a continuing problem, since half the children's sleepware sold between July 1973 and April 1977 was treated with this chemical. (25 refs.)

78-5167 **Mouse Skin Carcinogenicity Tests of the Flame Retardants Tris(2,3-dibromopropyl)phosphate, Tetrakis(hydroxymethyl)phosphonium Chloride, and Polyvinyl Bromide.** (Eng) Van Duuren, B. L. (Lab. Organic Chemistry and Carcinogenesis, Inst. Environmental Medicine, New York, NY, 10016); Loewengart, G.; Seidman, I.; Smith, A. C.; Melchionne, S. *Cancer Res* 38(10): 3236-3240; 1978.

The flame retardants tris(2,3-dibromopropyl)phosphate (tris), tetrakis(hydroxymethyl)phosphonium chloride (THPC), and polyvinyl bromide (PVB) were tested for carcinogenic activity by thrice weekly skin application in female Icr/Ha Swiss mice for 420-496 days. Tris, at doses of 30 or 10 mg/application (30 mice/group), induced benign and malignant tumors of the skin, forestomach, and oral cavity (tongue and gingiva) in a statistically significant number of mice ($p < 0.0005$). A statistically significant incidence of papillary tumors of the lung was observed at both doses ($p < 0.0005$). One carcinoma of the liver was observed at both doses, and the higher dose also resulted in a tubular adenocarcinoma of the kidney in one mouse. THPC (2 mg/application, 60 mice) and PVB (0.1 ml latex suspension/application, 30 mice) were inactive. PVB was also injected sc (approx 23 mg) into the mice once weekly for 48 wk; the mice were observed for an additional 12 wk. Liposarcomas were induced in 19/30 mice; the tumors were ascribed to physical carcinogenesis because the aqueous suspension contained 90% solids. The internal tumors observed in the PVB-treated animals were not significantly different from those observed in controls. (28 refs.)

-5168 **Host-Cell Reactivation of UV-irradiated and Chemically-treated Herpes Simplex Virus-1 by roderma Pigmentosum, XP Heterozygotes and Normal in Fibroblasts.** (Eng) Selsky, C. A. (Lab. Radiobiology, pt. Physiology, Harvard Sch. Public Health, Boston, MA, 115); Greer, S. *Mutat Res* 50(3): 395-405; 1978.

further characterize the xeroderma pigmentosum (XP) enotype, the survival of UV-irradiated herpes simplex us type 1 (HSV-1) strain MP was compared with the sur- al of N-acetoxy -2- acetylaminofluorene (NAcO- AF)-treated virus in normal human skin fibroblasts, cells from the different genetic complementation ups, an XP variant, and two presumed XP heterozygotes. addition, the survival of NAcO-AAF-treated HSV-1 MP s compared with that of nitrogen mustard-treated virus in mplementation group D XP cells. The relative ability of cells from the different complementation groups to reacti- e UV-irradiated virus was in the order D < C < B, and relative reactivation ability of these cells for AcO-AAF-treated virus was in the order D approx equal A < B < C. The survival of UV-/and NAcO-AAF-treat- HSV 1 MP in the XP variant was similar to that of treated us in normal fibroblasts. Caffeine in the postinfection assay dium had no effect on the results. Relative to normal skin roblast strains, groups A and B XP cell strains showed icient reactivation of virus treated with up to 100 μg AcO-AAF/ml. The inactivation kinetics of the treated us in the XP heterozygotes were the same as those in nor- l cell strains. UV and NAcO-AAF treatment resulted in uced virus survival in the XP cells relative to normal cells, ereas the survival of nitrogen mustard-treated virus was ilar in group D XP cells and normal fibroblasts. The data icate that UV- and NAcO-AAF-treated virus is repaired the same pathway or by different pathways that share a nmon intermediate step and that the excision defect of XP s plays little if any role in the reactivation of nitrogen stard-treated virus. (24 refs)

5169 **Xeroderma Pigmentosum: Damage to DNA Is Involved in Carcinogenesis.** (Eng) Setlow, R. B. ology Dept., Brookhaven Natl. Lab., Upton, NY, 11973); med, F. E.; Grist, E. *In: Mechanisms of Carcinogenesis. ceedings of the Cold Spring Harbor Conferences on Cell liferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. ld Spring Harbor: Cold Spring Harbor Laboratory): Ori- s of Human Cancer. Vol. 4 (Book B), 699 pp.; 889-902; 7.

The role of UV in skin cancer was studied with the use of human fibroblasts from normal individuals, and from patients with xeroderma pigmentosum (XP). Cells were treated with acetoxyacetylaminofluorene (AAAF) and/or UV. DNA was isolated and then treated with an endonuclease from *Micrococcus luteus*, which recognizes UV- but not AAAF-induced DNA damage. AAAF treatment did not inhibit the removal of sites sensitive to *M. luteus* endonuclease, as would be expected if AAAF damage truly mimicked UV damage. It is concluded that the enzymatic steps involved in the repair of the two types of damage are not identical and that the defect in XP cells controls more than one function. The defect may be at the level of formation or stability of the presumptive repair complex involved in excision repair. In a study of postreplication repair, cells were preilluminated with an inducing exposure of 2.5 joules (J)/m^2 of 254-nanometer UV radiation. After 2.8 or 14 hr, the cells were treated with a second exposure of 5.0 J/m^2 and, 15 min later, the DNA was pulse-labeled with ^{3}H-thymidine. Postreplication repair was enhanced in all the cells tested, but it was much larger in XP variant cells than in normal or conventional XP cells. In cells from XP-variant individuals, excision is normal, but postreplication repair is slow. It is inferred that in these cells the probability of a carcinogenic event is high not because many dimers remain, but because replication past a dimer is more error-prone than the process in normal cells. (41 refs)

78-5170 **A Mutagen Screening Test for UV-Mimetic Chemicals Based on Differential Killing of Human Cell Lines (Meeting Abstract).** (Eng) Burrell, A. D. (General Products Div., IBM Corporation, San Jose, CA, 95193); Anderson, J. J. *Mutat Res* 53(2): 161; 1978. (2 refs)

78-5171 **Mutational Synergism of Nitrous Acid and Ultraviolet Light (Meeting Abstract).** (Eng) Kubitschek, H. E. (Div. Biological and Medical Res., Argonne Natl. Lab., Argonne, IL). *Mutat Res* 53(2): 214-215; 1978. (no refs)

78-5172 **Excision Repair of Ultraviolet Damage in Mammalian Cells: Evidence for Two Steps in the Ex-**

cision of Pyrimidine Dimers. (Eng) Williams, J. I. (Dept. Pathology, Stanford Univ. Medical Center, Stanford, CA, 94305); Cleaver, J. E. *Biophys J* 22(2): 265-279; 1978.

The post-UV irradiation incidence of pyrimidine dimer formation and the kinetics of DNA repair in African green monkey kidney CV-1 cells were studied by measuring survival; T4 endonuclease V-sensitive sites; the fraction of pyrimidine dimers in acid-insoluble DNA, as determined by thin layer chromatography (TLC); and repair replication. The CV-1 cells demonstrated a survival curve with extrapolation number $n = 7.8$ and D_0 (the single dose of radiation necessary to kill 63% of the cells using the straight part of the cell survival curve) of 2.5 joules/m^2. Pyrimidine dimers were lost from acid-insoluble DNA more slowly than endonuclease-sensitive sites were lost from or new bases were incorporated into high-mol-wt DNA during the course of repair. Addition of ^{3}H-thymidine to the cultures of x-irradiation (2 or 10 kilorads) 24 hr before UV irradiation had no effect on repair replication induced by UV (25 joules/m^2). These findings suggest that pyrimidine dimer excision measurements by TLC are probably not affected by radiation from high levels of incorporated radionuclides. The endonuclease-sensitive site and TLC measurements can be reconciled by the assumption that pyrimidine dimers are excised from high mol wt DNA in acid-insoluble oligonucleotides that are slowly degraded to acid-soluble fragments. Since the CV-1 cell line is often used as a host for simian virus 40 or herpesvirus studies, these findings provide biochemical information valuable in the study of host cell reactivation and viral mutagenesis. (57 refs)

78-5173 **Mechanisms of Depressed Reactivity to Dinitrochlorobenzene and Ultraviolet-induced Tumors During Ultraviolet Carcinogenesis in BALB/c Mice.** (Eng) Jessup, J. M. (Dept. Surgery, Univ. Texas Medical Sch. at Houston, Houston, TX, 77025); Hanna, N.; Palaszynski, E.; Kripke, M. L. *Cell Immunol* 38(1): 105-115; 1978.

Experiments were conducted to determine (1) whether UV radiation renders BALB/cAnN female mice susceptible to challenge with a highly antigenic, syngeneic, UV-induced fibrosarcoma (2C16) and (2) whether chronic UV radiation induces a transient, reversible depression of dinitrochlorobenzene (DNCB) hypersensitivity in these mice. Mice were irradiated (av dose rate, 2.8 joules/m^2/sec) for 1 hr, 3x/wk, for 1-4 mo. Upon transplantation, fibrosarcoma 2C16 grew progressively in 9/10 mice irradiated for 1 mo, 7/10 irradiated for 2 mo, and 10/10 irradiated for 3 mo. The lack of tumor rejection in the irradiated mice could be transferred with the spleen cells to lethally x-irradiated syngeneic recipients. Groups of UV-treated and untreated mice were sensitized with DNCB at monthly intervals after the initial UV treatment, and their responses were compared with those of unsensitized mice in a footpad assay. UV-treated mice failed to exhibit a primary immune response to DNCB for the first 2 mo of irradiation. However, mice irradiated for 3 or 4 mo could be sensitized, and they exhibited the same levels footpad reactivity as sensitized controls. The two i munologic dysfunctions demonstrated are mediated by diff ent mechanisms, even though both are induced by UV radi tion. The inability of UV-treated mice to reject UV-induc tumors seems to be due, at least in part, to the developme of specific suppressor cells, probably, T lymphocytes. T temporary inability of UV-treated mice to respond to DN seems to be due to a block in antigen processing or presen tion, since DNCB-reactive lymphocytes can be demonstrat in these animals by passive transfer studies. (14 refs)

78-5174 **Ultraviolet Carcinogenesis in T-Cell-deplet Mice.** (Eng) Norbury, K. C. (Merck Inst. The peutic Res., West Point, PA, 19486); Kripke, M. L. *J N Cancer Inst* 61(3): 917-921; 1978.

The induction of skin tumors by chronic UV irradiation w compared in normal C3H/HeN(MTV-) mice, T-cell-deplet mice, and T-cell-depleted mice reconstituted with thym grafts. The T-cell-depleted mice were thymectomized young adults, lethally x-irradiated, and repopulated w neonatal liver cells. All mice were irradiated (dose rate, joules/m^2/sec, wavelength range 280-320 nanometers) min 3x/wk for 3 wk, then 60 min 3x/wk until tumor develo ment. Skin tumors appeared earlier in the immunosuppress T-cell-depleted mice (50% tumor incidence, 30 wk) than the normal mice (35 wk). However, tumors developed m rapidly in the group that was T-cell-depleted and immunol ically restored with thymus grafts (24 wk). In the lat group, most of the tumors were squamous cell carcinom whereas in the normal mice, fibrosarcomas predominat These experiments illustrate the limitations of this approa to studying the role of the immune response in carcinoge sis. (26 refs.)

78-5175 **Ultraviolet Radiation-induced Chromoson Abnormalities in Fetal Fibroblasts from N Zealand Black Mice.** (Eng) Reddy, A. L. (Medical Genet Section, Medical Service, Veterans Admin. Hosp., 4435 B con Ave. S., Seattle, WA, 98108); Fialkow, P. J.; Salo, *Science* 201(4359): 920-922; 1978.

Cultured fetal fibroblasts from New Zealand Black (NZ and BALB/c mice were exposed to 8,16,or 32 joules (J)/m of UV radiation, and the incidence of chromosome (c breaks and rearrangements was determined. Chr abnorm ties were found more often in untreated NZB cells than BALB/c cells, but the difference was not significant. Af irradiation with 8 and 16 J/mm^2, the number of aberrati did not increase in the BALB/c fibroblasts; in contrast, numbers of chromatid and chr breaks and interchanges creased significantly in the NZB fibroblasts. There was a rect relation between the frequency of abnormal cells a radiation dose: at the lower doses, chr abnormalities w

creased only in NZB cells, but at 32 J/mm², both NZB and ALB/c cells exhibited a high incidence of abnormalities. At is dose, however, significantly more abnormal cells were und in the former (57%) than in the latter (26%). The umber of abnormal cells was max at 24 hr after radiation d then decreased to untreated levels at 72 hr. This temporal ecline may be due to reproductive death of the abnormal lls consequent to chr damage. Thus, fibroblasts from NZB tuses manifest increased sensitivity to UV radiation. This r instability is similar to that reported for cells from roderma pigmentosum patients, and it may be related to e aneuploid clones and lymphoreticular malignancy char-teristic of adult NZB mice. Chr instability may favor the velopment of specific chr changes that, in turn, play a role the evolution of neoplasia. (13 refs.)

-5176 **Fluorescent Light-induced DNA Crosslinkage and Chromatid Breaks in Mouse Cells in Cul-re.** (Eng) Gantt, R. (Lab. RNA Tumor Viruses, NCI, Be-esda, MD, 20014); Parshad, R.; Ewig, R. A.; Sanford, K. .; Jones, G. M.; Tarone, R. E.; Kohn, K. W. *Proc Natl Acad i USA* 75(8): 3809-3812; 1978.

e effect of cool-white fluorescent light (20 hr exposure to 6 W/m²) on the DNA and chromosomes of cultured mouse mbryo and lung cells was studied. Compared with shielded lls, the exposed cultures showed a significant increase in e percentage of cells with chromatid breaks and in the num-r of chromatid breaks per cell. The breaks appeared to be ll density-dependent. The number of minute chromosomes d the number of chromatid exchanges per cell were signifi-ntly increased in the exposed cultures. The fluorescent light d no apparent effect on the frequency of metacentric romosomes. In Kohn's alkaline elution assay, the DNA om exposed cells eluted more slowly than that from shield-cells, suggesting that the DNA in the exposed cells was larger mol wt and cross-linked. The estimated frequency crosslinks was sufficient to account for the observed num-r of chromatid breaks. The data suggest that the DNA oss-linking and chromosome aberrations produced by orescent light may be related. (19 refs.)

-5177 **Effect of Radiation Dosage on the Synergism Between Radiation and Estrogen in the Produc-n of Mammary Cancer in the Rat.** (Eng) Segaloff, A. (Div. s., Alton Ochsner Medical Foundation, 1516 Jefferson ghway, New Orleans, LA, 70121); Pettigrew, H. M. *Can-Res* 38(10): 3445-3452; 1978.

e effect of radiation dosage on the synergism between iation and estrogen in the production of mammary cancer s studied in A x C rats. Rats that had previously been terectomized were exposed to estrogen by implantation 0-mg cholesterol pellets containing 25% diethylstilbestrol ES). The left mammary chain of the rats was then exposed to 50, 150, or 450 rads of x-radiation while the rats were anesthetized with urethan or sodium pentobarbital. Control animals were implanted with cholesterol pellets containing no DES or they were not implanted at all. Some of the animals died in the 24 hr following irradiation; these deaths were independent of the anesthetic used, but there was a positive dose-response curve for radiation. In terms of median survival time, the highest radiation doses produced the shortest survival times, and rats receiving estrogen also had the shortest survival times. Overall growth was also inhibited by both of the agents used. With radiation alone, there was an increase in benign tumors with a dose-response curve, but the increase in mammary cancers was not significantly proportionate to dose. There was no significant difference in tumor incidence in any of the glands in each mammary chain. The cholesterol carrier did not affect the synergism between estrogen and radiation for mammary carcinogenesis; however, synergism between radiation and DES was apparent. Malignant mammary tumors were relatively rare in groups that did not receive DES. The optimal expression of synergism was dependent on the amount of radiation given. (23 refs.)

78-5178 **Second Malignancies of the Irradiated Area in Patients Treated for Uterine Cervix Cancer.** (Eng) Czesnin, K. (Dept. Gynecologic Oncology, Inst. Oncology in Warsaw, P.O. Box 47, Warsaw 02-034, Poland); Wronkowski, Z. *Gynecol Oncol* 6(4): 309-315; 1978.

The incidence of second malignancies in the irradiated area was analyzed in 8,043 patients with carcinoma of the uterine cervix treated primarily by irradiation between 1948 and 1966 at the Institute of Oncology in Warsaw, Poland. Radiotherapy had been administered by the modified Paris technique (dose to point A = 5,500 rads, point B 1,500 rads) and irradiation from external fields (deep field dose of x-rays = 3,000 R; ^{60}Co = 3,500-4,500 R). Follow-up time ranged from 9 to 27 yr; 4,041 patients survived 5 yr. Second malignancies developed in the irradiated area of 28 women 18 mo-22 yr after primary treatment. The most frequent type of second neoplasm was cancer of the uterine corpus, followed by ovarian cancer, cancer of the vulva, cancer of the large bowel and rectum, and malignant neoplasms of the integument. Uterine corpus cancers occurred after the longest period of time (13 yr after therapy); cancer of the vulva and bladder and sarcoma of the uterine corpus occurred in a shorter period of time (6 yr after therapy). The incidence rates for uterine sarcoma and soft tissue malignant neoplasms in the irradiated area were significantly higher in the examined group than the rates expected for the whole population. No significant increase in incidence rates for other pelvic neoplasms was demonstrated. (22 refs.)

78-5179 **Sebaceous Carcinoma of the Eyelid Following Radiation Therapy.** (Eng) Lemos, L. B.

(Memorial Sloan-Kettering Cancer Center, New York, NY); Santa Cruz, D. J.; Baba, N. *Am J Surg Pathol* 2(3): 305-311; 1978.

A 12-yr-old boy developed a metastatic sebaceous carcinoma of the eyelid 11 yr after curative radiation therapy for bilateral retinoblastoma. The right eye had been enucleated at the age of 15 mo; the right orbit was then treated with 2,100 rads and the left eye with 1,475 rads. The gross and ultrastructural pathologic findings are presented. A review of the literature revealed only five reports of sebaceous carcinoma associated with previous irradiation. Three of the patients had been treated for benign disorders, and two for bilateral retinoblastoma. This small series of six cases suggests a cause-and-effect relationship between irradiation and sebaceous carcinoma. However, the possibility that genetic factors may predispose patients with bilateral retinoblastoma to develop sebaceous carcinoma cannot be excluded. (31 refs.)

78-5180 **Postirradiation Fibrosarcoma Following Radical Mastectomy.** (Eng) Iwasaki, K. (Dept. Surgery I, Kyushu Univ. Faculty Medicine, Fukuoka, Japan); Nagamitsu, S.; Tsuneyoshi, M. *Jpn J Surg* 8(1): 73-77; 1978.

A 52-yr-old women underwent radical mastectomy for Stage I infiltrating breast carcinoma followed by radiation therapy (2,500 rads 20 days later). Over the next 11 yr, five fibrosarcomas arose from the mastectomy scar that were considered to be a result of the radiation therapy. (8 refs)

78-5181 **Radioactive Fallout Effects of the Nagasaki Atomic Bomb.** (Eng) Okajima, S. (Dept. Radiation Byophysics, Atomic Disease Inst., Nagasaki Univ. Sch. Medicine, Nagasaki, Japan); Takeshita, K.; Antoku, S.; Shiomi, T.; Russell, W. J.; Fujita, S.; Yoshinaga, H.; Neriishi, S.; Kawamoto, S.; Norimura, T. *Health Phys* 34(6): 621-633; 1978.

Whole-body counting techniques, physical and laboratory examinations, and chromosome studies were used to determine retained radionuclide activity and late radiation effects in Nishiyama residents exposed to fallout from the Nagasaki atomic bomb. Soil, reservoir sediments, and crops from Nishiyama and comparison areas were examined for ^{137}Cs content by scintillation counting. Body ^{137}Cs concentrations were significantly higher among those exposed to the fallout than among those who were not exposed. However, the av annual exposure dose was low compared with the dose limit recommended by the ICRP, and no deleterious effects were evident. The body burden of ^{137}Cs in the Nishiyama residents was maintained by constant replenishment via ingestion of contaminated farm products. The ^{137}Cs content of the drinking water used by Nishiyama residents was essentially the same as that of the Nagasaki City and the Nishiyama and Urakami reservoirs. (32 refs.)

78-5182 **X-ray Sensitivity of Diploid Fibroblasts fro Patients with Hereditary or Sporadic Retin blastoma.** (Eng) Weichselbaum, R. R. (Laboratory Radiob ology, Dept. Physiology, Harvard Univ., Sch. Public Healt Boston, MA, 02115); Nove, J.; Little, J. B. *Proc Natl Aca Sci USA* 75(8): 3962-3964; 1978.

The x-ray sensitivity, expressed D_0 values, of diploid fibro lasts from six patients with hereditary retinoblastoma, seve patients with sporadic retinoblastoma, a retinoblastoma p tient with a D-deletion of chromosome 13, and four norm controls was studied. Cultured fibroblast cells were expose to an x-ray dose of 80/rads/min and fixed and stained 15 da later; colonies composed of more than 50 cells were scor as survivors. The mean D_0 (inverse of the slope) of the x-r survival curves was significantly lower for the heredita group than for the sporadic group. Cells from a patient b longing to a family with an extremely high incidence of mali nant tumors appeared to be considerably more x-ray sensiti than those from other hereditary patients. Only one here tary strain was more resistant than the most sensitive spora ic strain, the sensitivity of most of the sporadic strains bei well within the normal range. The fibroblasts from the patie with the D-deletion were not significantly x-ray sensitive. T increased radiosensitivity of hereditary retinoblastoma broblasts could result from a defect in a molecular DN repair process. (17 refs.)

78-5183 **Liver Cell Proliferation and Failure of X Radi tion to Produce Hepatomas in Rats.** (En Christov, K. (Acad. Medicine, Natl. Inst. Oncolog Sofia-56, Darvenitza, Bulgaria). *Radiat Res* 74(2): 378-38 1978.

X-ray doses that are carcinogenic in mice failed to indu hepatomas in intact or partially hepatectomized male Wist rats. In contrast, hepatoma incidence was increased in r treated with dimethylnitrosamine during late G_1. This diff ence could result from different mechanisms of chemical a radiation carcinogenesis in the liver. (11 refs)

78-5184 **A Compartment Model of Plutonium Dynami in a Deciduous Forest Ecosystem.** (Eng) Ga en, C. T. (Environmental Sciences Div., Oak Ridge Na Lab., Oak Ridge, TN, 37830); Gardner, R. H.; Dahlman, C. *Health Phys* 34(6): 611-619; 1978.

An ecosystem model of plutonium (^{239}Pu and ^{240}Pu) behavi in a contaminated deciduous forest is described. The mod was formulated as a linear compartment model with d nor-controlled flows between compartments. It emplo time-variant transfer coefficients. At steady states predict by the models, the amount of Pu in the biota is $<0.25\%$ the existing inventory in the soil. The soil would be the maj

pository of Pu in the forest, and reciprocal exchanges of u between soil and litter or soil and tree roots would be the ominant factors affecting the Pu ecosystem distribution. owever, the av predicted amount of Pu in each forest eco- stem, given a uniform soil contamination, could vary de- ending on site conditions and forest species composition. resent attempts to model Pu dynamics in terrestrial ecosys- ms are hampered by uncertainties in predictions arising om problems with system identification, quality of available ta, and a lack of validation. The ability to develop reliable odels of Pu transport in ecosystems will improve with more ecise data from natural environments and a better under- anding of the sources of variation in Pu data. (24 refs.)

8-5185 **Late Effects of Inhaled $Pu(NO_3)_4$ in Rats (Meeting Abstract).** (Eng) Ballou, J. E. (Bat- le, Pacific Northwest Labs., Richland, WA, 99352); Dagle, E.; McDonald, K. E. *Health Phys* 33(6): 665-666; 1977. o refs)

78-5186 **Trauma and Brain Tumors: An Experimental Study (Meeting Abstract).** (Eng) Morantz, R. A. (Univ. Kansas Medical Center, Kansas City, KS); Shain, W. *J Neuropathol Exp Neurol* 37(5): 662; 1978. (no refs)

78-5187 **Genetic Analysis of the Defectiveness in Strain MC29 Avian Leukosis Virus.** (Eng) Bister, K. (Institut fur Virologie, Zentrum fur Hygiene, Universitat Freiburg, 78 Freiburg, W. Germany); Vogt, P. K. *Virology* 88(2): 213-221; 1978.

The nature of the replication defect of avian myelocytomatosis virus (MC29) was analyzed in complementation experiments, in which the replicative genes (*gag*, *pol*, *env*) were tested genetically. Continuous nonproducer (NP) Japanese quail cell lines transformed by MC29 were superinfected with various helper viruses. Infectious MC29 pseudotypes were formed only with viruses related to the avian leukosis-sarcoma complex (Rous-associated virus type 1 or ring-necked pheasant virus), which demonstrated that its replication defect is not restricted to a lack of envelope glycoprotein. Reticuloendotheliosis virus, golden pheasant virus, or an amphotrophic murine leukemia virus (MuLV-1313) could not rescue MC29 from the NP cells, but they complemented the envelope-defective Bryan high-titer strain of Rous sarcoma virus (RSV-B). Analysis of the host range and viral interference patterns of MC29 rescued from NP clones indicated that both are determined by the envelope specificity of the activating helper virus. Co-cultivation or Sendai virus-induced fusion of MC29 NP cells with quail or White Leghorn C/BE chicken cells transformed by RSV-B did not result in complementation of the defects in either virus: fluorescent antibody staining did not detect virus-specific antigens at the surface of the MC29 NP cells. Temperature-sensitive mutants of RSV with lesions in the genes coding for RNA-directed DNA polymerase (*pol* gene) or nonglycosylated structural proteins (*gag* gene) did not acquire wild-type characteristics when grown in the NP cells. These experiments indicate that MC29 is defective in all three genes essential for retrovirus replication; ie, *gag*, *pol*, and *env*. These defects may be significant for the origin of the retroviruses and for their oncogenic activities. (48 refs.)

78-5188 **In Vitro Synthesis of a Functional Avian Sarcoma Virus Transforming-Gene Product.** (Eng) Erikson, E. (Dept. Pathology, Univ. Colorado Medical Center, Denver, CO, 80262); Collett, M. S.; Erikson, R. L. *Nature* 274(5674): 919-921; 1978.

The in vitro product of the Schmidt-Ruppin avian sarcoma virus (ASV, subgroup D) *src* gene was tested for phosphotransferase activity. The 70S RNA was extracted from nondefective (nd) and transformation-defective (td) virions and then purified and fractionated. The RNA in fractions 12-15 was used to program messenger RNA-dependent reticulocyte lysates. The ^{35}S-methionine-labeled polypeptide products were analyzed by gel electrophoresis, and the resul indicated that p60src was translated only from nd RNA. N p60src was translated from td RNA, although this RN stimulated protein synthesis 9-fold above the backgrour synthesis without RNA, compared with 10-fold stimulatic with nd RNA. Serum from rabbits bearing ASV-induced t mors (TBR serum) precipitated p60src and a small amou of Pr76 (product of ASV *gag* gene) from the products synth sized in response to nd RNA; in addition, a small amou of Pr76 was found in the immunoprecipitate of the produc synthesized in response to td RNA. Only the products translation of the RNA that immunoprecipitated with TB serum yielded phosphorylated IgG. The translation of vir RNA in vitro resulting in the synthesis of an enzymatical functional p60src strongly indicates that the product of t *src* gene is a protein kinase. These and other results show th p60src is a product of the ASV transformation gene in vit and in vivo and that its function is likely to result in t phosphorylation of cellular proteins. (12 refs.)

78-5189 **Inhibition of Reverse Transcription of 70S a 35S Avian Myeloblastosis RNAs by Nonprim tRNA's.** (Eng) Yamaura, I. (Sloan-Kettering Inst. Canc Res., Walker Lab., Rye, NY, 10580); Cavalieri, L. F. *J Vir* 27(2): 300-306; 1978.

The kinetics of the reverse transcription of 70S and 35S RN of avian myeloblastosis virus (AMV) was studied in the pre ence and absence of various transfer RNA's (tRNA's). A tRNA's inhibited synthesis due to the binding of tRNA's the polymerase. The reverse transcription kinetics of both 7 and 35S RNA's showed a complex inhibition pattern in t presence of nonprimer tRNA's obtained from 70S RN molecules. The nonprimer tRNA's that bound to the rever transcriptase decreased the affinity of the viral RNA for t enzyme. Thus, the binding of 70S or 35S RNA was decrease In contrast, tRNA's from *Escherichia coli* and yeast show classical noncompetitive inhibition: they bound reversib and randomly and did not alter the affinity of viral RNA f the polymera e. The max rate of synthesis with 70S RNA the template was less than that with 35S RNA, presumab because the former contains nonprimer tRNA's that can i teract with the polymerase. (18 refs.)

78-5190 **The Defectiveness of Mill Hill 2, a Ca cinoma-inducing Avian Oncovirus.** (Eng) Hu, S. (Dept. Microbiology, Univ. Southern California, Sc Medicine, 2011 Zonal Ave., Los Angeles, CA, 90033); Mo covici, C.; Vogt, P. K. *Virology* 89(1): 162-178; 1978.

he results of characterization experiments on the avian carinoma virus Mill Hill 2 (MH2) are presented. MH2 transormed avian fibroblast and macrophage cultures derived rom 10-day chick embryos, and it also transformed secondry cultures of macrophages from chick or Japanese quail mbryo yolk sacs. It was defective in replication and dependnt on a helper virus, MH2 associated-virus (MH2 AV), for ne production of infectious progeny. MH2 AV contained oth subgroup C and A envelope determinants; its helper inctions were required by MH2 in the *env*, *pol*, and probably ne *gag* genes. The defects of MH2 could be complemented nly by helper viruses of the chicken leukosis group, further iggesting that MH2 is defective in *gag* or *pol*, or both. MH2 ansformed-nonproducer cells synthesized an aberrant viral olyprotein of 100,000 daltons. This MH2p100 carried antienic determinants of the *gag* protein p27, but not of the *env* rotein gp85. MH2p100 was not cleaved into smaller, funconal proteins and was not glycosylated. (43 refs.)

8-5191 **Evidence for Splicing of Avian Sarcoma Virus 5′-terminal Genomic Sequences onto Viral-specific RNA in Infected Cells.** (Eng) Krzyzek, R. A. (Dept. licrobiology, Univ. Minnesota Medical Sch., Minneapolis, IN, 55455); Collett, M. S.; Lau, A. F.; Perdue, M. L.; Leis, P.; Faras, A. J. *Proc Natl Acad Sci USA* 75(3): 1284-1288; 978.

he 5′-terminal nucleotide sequences of the avian sarcoma irus (ASV) genome are transcribed by reverse transcriptase n vitro into a DNA transcript that represents the entire disnce (approx 100 nucleotides) between the transfer RNATrp RNATrp) primer molecule and the 5′ terminus. These DNA_{100} transcripts were used in hybridization reactions with SV-specific RNA from infected avian cells. Nucleotide seuences complementary to these transcripts were found on l the various size classes of viral messenger RNA (mRNA) entified. Similar hybridization results were obtained with specific DNA transcript complementary to viral genomic ucleotide sequences between the tRNATrp primer molecule id up to, but not including, the terminal redundant seuences (DNA_{70}), indicating that the observed hybridization DNA_{100} to all size classes of viral RNA in infected cells d not reflect hybridization of DNA_{100} to the terminal redunnt sequences at the 3′ end of the viral genome. *Escherichia oli* RNase H hydrolysis of RNA-DNA hybrids consisting genomic 35S RNA obtained from virus and DNA_{100} tranripts indicated that viral genomic sequences complemenry to these DNA transcripts were not present at sites distal the ends of the RNA genome and, therefore, not adjacent the corresponding gene sequences representing the various ecies of viral mRNA from infected cells. These findings ggest that the 5′-terminal genomic nucleotide sequences, a portion thereof, are somehow added or "spliced" onto ch ASV-specific mRNA species in infected cells either dur- or after transcription of proviral DNA. (35 refs)

78-5192 **The Effect of Infection and Transformation by Rous Sarcoma Virus upon Lysophosphoglyceride Biosynthesis in Chicken Embryo Fibroblasts.** (Eng) Edwards, R. G. (Div. Biochemical Virology and Membrane Res., Scheie Eye Inst., Univ. Pennsylvania Sch. Medicine, Philadelphia, PA, 19104); Blough, H. A. *Virology* 89(1): 314-317; 1978.

Lysophosphoglyceride biosynthesis was studied in secondary chicken embryo fibroblasts infected with the Schmidt-Ruppin strain (subgroup A) of Rous sarcoma virus (RSV) or its transformation-defective mutant (td_{105}) that lacks the *src* gene. The cells were infected with 5×10^6 focus-forming units of RSV or 5×10^5 to 5×10^6 infectious units of td_{105} and harvested 10 days later. De novo biosynthesis lysophosphoglycerides was greatly depressed in cells transformed by the wild-type virus but not in those infected with the mutant. This depression may be due to a lack of the appropriate enzyme, rather than to an inhibitory factor, and thus represent an effect of expression of the *src* gene on lipid biosynthesis. (9 refs.)

78-5193 **Rous Sarcoma Viral Protein p15 Induces Intracellular Processing of Viral Precursor pr76 (Meeting Abstract).** (Eng) von der Helm, K. (ISREC, CH-1066 Epalinges, Switzerland); Rungger, D.; Wille, W.; Willecke, K. *Experientia* 34(7): 942; 1978. (1 ref)

78-5194 **A Transformation Defective Mutant of Rous Sarcoma Virus Inducing Chick Embryo Neuroretinal Cell Proliferation.** (Eng) Calothy, G. (Fondation Curie, Institut du Radium, 91405 Orsay, France); Poirier, F.; Dambrine, G.; Pessac, B. *Virology* 89(1): 75-84; 1978.

A transformation-defective (*td*) Rous sarcoma virus (RSV) mutant was isolated using induction of chick embryo neuroretinal (NR) cell multiplication as a genetic marker. The mutant was derived from a variant of Schmidt-Ruppin RSV subgroup D (SR-RSV-D) that was rescued by Sendai-mediated fusion transformed chick embryo fibroblasts (CEF) with simian virus 40-transformed Lesch-Nyhan cells infected with SR-RSV-D. The mutant, designated *td* PA-101, induced sustained multiplication of NR cells from 7-day-old chick embryos. However, the mitogenic and transforming properties of the mutant were permanently dissociated in NR cells. *td*PA-101 was defective in transforming NR cells and CEF, and it did not produce sarcomas upon inoculation into white Leghorn chicks. Thus, this mutant represents a novel class of nonconditional RSV mutants that differ from other *td* viruses in retaining fully the capacity to induce NR cell proliferation. (31 refs.)

78-5195 **Differential Expression of Rous Sarcoma Virus-specific Transformation Parameters in Enucleated Cells.** (Eng) Beug, H. (Biologisch-Medizinische Abteilung, Max-Planck-Institut fur Virusforschung, 7400 Tubingen, W. Germany); Claviez, M.; Jockusch, B. M.; Graf, T. *Cell* 14(4): 843-856; 1978.

To obtain information about the primary site of action of the Rous sarcoma virus (RSV) *src* gene product(s), chicken embryo fibroblasts transformed with the Ta and *ts*68 mutants of RSV were enucleated and studied for their capacity to express reversibly the transformed phenotype in response to temperature changes. After shift to the permissive temperature (35 C), the cytoplasts acquired a transformed morphology and displayed characteristic ruffles and microvilli at their surface. Immunofluorescence revealed that they also lost their actin filament cables and exhibited characteristic changes in the pattern of cell-surface structures containing the large external transformation-sensitive (LETS) protein. Expression of all these transformation parameters was reversible after shiftback to the nonpermissive temperature (41 C). These results indicate that a whole set of changes characteristic of the transformed phenotype can be expressed independently of the cell nucleus. In contrast, *ts* mutant-infected cytoplasts were no longer able to respond to temperature shifts with changes in their hexose transport rate. Cytoplasts prepared from cells grown at 41 C retained their low rate of hexose uptake after shift to 35 C, but cytoplasts from cells grown at 35 C exhibited a high rate of hexose transport even after 10 hr of shift to 41 C. These findings agree with the hypothesis that the product of the RSV *src* gene represents a multifunctional protein that acts independently on nuclear and extranuclear sites. (51 refs.)

78-5196 **Suppression and Enhancement of Mitogen Response in Chickens Infected with Marek's Disease Virus and the Herpesvirus of Turkeys.** (Eng) Lee, L. F. (Regional Poultry Res. Lab., Science and Education Admin.-Federal Res., U.S. Dept. Agriculture, East Lansing, MI, 48823); Sharma, J. M.; Nazerian, K.; Witter, R. L. *Infect Immun* 21(2): 474-479; 1978.

The kinetics of the phytohemagglutinin (PHA) response of peripheral blood lymphocytes from chickens infected with oncogenic Marek's disease virus (MDV) or nononcogenic herpesvirus of turkeys (HVT) was studied using a whole-blood microassay. Approx 7 days after inoculation, the PHA response was depressed in MDV-inoculated resistant line N or susceptible line 7_2 chickens and in HVT-inoculated line 7_2 chickens. All chickens initially regained their PHA responsiveness. Susceptible chickens that died of MD or developed MD lymphoma in later stages of virus infection showed a second severe depression in the PHA response. No depression was observed in HVT-vaccinated chickens when challenged with MDV. The PHA response of MDV-inoculated chickens that survived MD, HVT-inoculated chickens, and HVT-vaccinated MDV-challenged chickens showed e dence of enhancement. The depression of the PHA respor was attributed to the suppressive effect of macrophages T-cell response. This finding is consistent with the results previous studies on MDV suppression of the PHA respon (27 refs.)

78-5197 **Identification of an Abelson Murine Leuken Virus-encoded Protein Present in Transform Fibroblast and Lymphoid Cells.** (Eng) Witte, O. N. (De Biology, Massachusetts Inst. Technology, Cambridge, M 02139); Rosenberg, N.; Paskind, M.; Shields, A.; Baltimo D. *Proc Natl Acad Sci USA* 75(5): 2488-2492; 1978.

A search for gene products in Abelson murine leukemia vi (A-MuLV)-transformed cells that could play a role in tra formation revealed that extracts from A-MuLV-transform lymphoid and fibroblast cell lines contained a protein wi a mol wt of 120,000 daltons (P120). Immunoprecipitati with specific sera indicated that P120 contained regio homologous to the 5′-terminal segment of the MuLV g gene complex (p15, p12, and at least part of p30), but it lack detectable determinants of p10, reverse transcriptase, and t envelope glycoprotein. P120 was phosphorylated and had intracellular half-life of 3-6 hr. In vitro translation of viri RNA from A-MuLV, with Moloney MuLV as helper, yie ed a 120,000-dalton product with serological reactivity sir lar to that of cellular P120. Translation of the RNA from t helper produced no P120. P120 was expressed in A-MuLV-transformed lymphoid and fibroblastic lines teste but it was not detectable in a lymphoid line in which t A-MuLV genome was established by infection but was n responsible for the transformation. Expression of P120 w selectively retained in clones of A-MuLV-transformed ly phocytes that converted to a nonproducer state after loss expression of helper MuLV intracellular precursors. The findings suggest that the P120 product of the A-MuL genome may be responsible for maintenance of the tra formed phenotype of lymphoid and fibroblast cells tra formed by the virus. (28 refs)

78-5198 **Abelson Virus-induced Lymphomagenesis Mice.** (Eng) Risser, R. (McArdle Lab. Canc Res., Univ. Wisconsin, Madison, WI, 53706); Potter, M Rowe, W. P. *J Exp Med* 148(3): 714-726; 1978.

The age- and virus-dose-dependence of Abelson murine le kemia virus (MuLV-A) lymphomagenesis and the pattern susceptibility of various mouse strains to MuLV-A were e amined. MuLV-A lymphoma induction was age-depende virus-dose-dependent, and under the control of host ge unrelated to other genes known to control murine leuke (*Fv-1* or *Fv-2*). The most common sites of lymphoma we

ıe vertebral regions and skull, frequently resulting in the ıaracteristic caput previously described for Abelson disease. f 16 mouse strains tested, only BALB/c and some of its erivative strains showed high sensitivity to MuLV-A infecon. Studies with CXB (BALB x B6) recombinant inbred rains and hybrids between them suggest that BALB/c carıes dominant sensitivity alleles at two loci, tentatively desigated *Av-1* and *Av-2*, which confer on these mice partial susptibility to MuLV-A lymphoma induction. In addition, the *-2* gene may play a minor role in determining the ısceptibility of mice to MuLV-A, its effect being en only in mice homozygous for resistance at both *v-1* and *Av-2*. Virologic studies indicate that the sistance of adult B6 mice is not related to restriction n the helper virus replication, but is specific for the efective transforming virus genome. (25 refs)

8-5199 **Cells Nonproductively Transformed by Abelson Murine Leukemia Virus Express a High lolecular Weight Polyprotein Containing Structural and onstructural Components.** (Eng) Reynolds, F. H. (NCI, rederick Cancer Research Center, Frederick, MD, 20014); acks, T. L.; Deobagkar, D. N.; Stephenson, J. R. *Proc Natl cad Sci USA* 75(8): 3974-3978; 1978.

ell clones nonproductively transformed by the replicaon-defective Abelson strain of murine leukemia virus A-MuLV) were analyzed for C-type viral antigen expression y competition immunoassay. AbLV-transformed mink nonroducer lines expressed a 110,000- to 130,000-mol-wt polyrotein containing MuLV gag proteins p15 and p12 covalent- linked to nonstructural A-MuLV-coded component(s) of pprox 80,000-100,000-mol-wt. This polyprotein lacked dectable antigenic cross-reactivity with other virion-coded ag gene proteins such as p30, p10, viral reverse transcriptase, nd gp70. The results suggest that a portion of this polyrotein might represent the A-MuLV *src* gene product and iat in translation, it is initially linked in precursor form to ag structural proteins. Superinfection of mink cells nonprouctively transformed by A-MuLV with a wild mouse amhotropic type C virus isolate, 4070-A, or the endogenous cat irus RD114 led to the production of pseudotype virus conining high concentrations of the A-MuLV-coded precursor olyprotein. (41 refs.)

8-5200 **Abelson Antigen: A Viral Tumor Antigen That Is Also a Differentiation Antigen of BALB/c lice.** (Eng) Risser, R. (McArdle Lab. Cancer Res., Univ. Visconsin, Madison, WI, 53706); Stockert, E.; Old, L. J. *Proc atl Acad Sci USA* 75(8): 3918-3922; 1978.

he hypothesis that Abelson murine leukemia virus A-MuLV) induces a cell surface antigen cross-reactive with ne normally present only in uninfected BALB/c mice was sted. Serum from C57BL/6 mice hyperimmunized with syngeneic A-MuLV lymphoma cells was cytotoxic for the immunizing cells. Using this reaction as a serologic test system for recognition of A-MuLV antigens, two serologic specificites were detected by absorption analysis with 40 tumors and 21 cell lines; (1) Friend-Moloney-Rauscher antigen(s) related to the Moloney MuLV helper and (2) an antigen expressed on all cells transformed by A-MuLV. The A-MuLV-specific antigen was also present on uninfected cells from BALB/c bone marrow, spleen, and fetal liver, but not cells from adult liver, thymus, lymph nodes, or peripheral blood. Abelson antigen was not expressed on bone marrow or spleen cells of 12 other murine strains. The Abelson antigen may be an antigenic determinant specified by a gene of BALB/c mice that was incorporated by recombination into the Moloney MuLV genome. (34 refs.)

78-5201 **Murine Leukemia Virus (T-8)-transformed Cells: Identification of a Precursor Polyprotein Containing *gag* Gene-coded Proteins (p15 and p12) and a Nonstructural Component.** (Eng) Sacks, T. L. (Lab. RNA Tumor Viruses, NCI, Bethesda, MD, 20014); Reynolds, F. H.; Deobagkar, D. N.; Stephenson, J. R. *J Virol* 27(3): 809-814; 1978.

Mink cells nonproductively transformed by the T-8 strain of mink cell focus-inducing virus, Abelson leukemia virus (AbLV), Moloney murine sarcoma virus (M-MSV), or the S+L- isolate of MSV were analyzed for high-mol-wt polyproteins. Cells transformed by T-8 or AbLV expressed the two amino terminal murine leukemia virus (MuLV) *gag* gene-coded proteins p15 and p12, but not the remaining *gag* gene-coded proteins p30 and p10, the *env* gene product gp70, or the reverse transcriptase. Virus-coded polyproteins of around 90,000 to 110,000 and 110,000 to 130,000 mol wt were demonstrated in T-8- and AbLV-transformed mink cells, respectively, by gel filtration and by immunoprecipitation followed by gel electrophoresis. In both cases, these proteins were precipitated by sera against Rauscher MuLV or M-MuLV, but not by control sera or by high-titered sera against MuLV gp70. To date, identification of high-mol-wt virus-coded precursor polyproteins containing structural and nonstructural components has been limited to those transforming viruses coding only for p15 and p12. (27 refs)

78-5202 **Cell-free Synthesis of Rauscher Murine Leukemia Virus "gag" and "gag-pol" Precursor Polyproteins from Virion 35 S RNA in a mRNA-dependent Translation System Derived from Mouse Tissue Culture Cells.** (Eng) Murphy, E. C. (Dept. Biology, Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030); Arlinghaus, R. B. *Virology* 86(2): 329-343; 1978.

The capacity of 35S genomic RNA from Rauscher leukemia

virus (RLV) to code for the synthesis of viral proteins was examined using a messenger RNA (mRNA)-dependent cell-free protein synthesis system derived from mouse tissue culture cell extracts by treatment with micrococcal nuclease. Analysis of the polypeptide product by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) indicated that RLV 35S RNA directed the synthesis of RLV-specific polypeptides of 55,000, 65,000, 75,000 and 200,000 apparent mol wt, identical in size to the known intracellular precursors of RLV mature polypeptides. None of the individual mature virus proteins appeared to be synthesized. When canavanine, an arginine analog, was substituted for arginine under conditions for cell-free protein synthesis, a RLV-specific polypeptide with a mol wt of approx 80,000 was synthesized at the expense of the 65,000- and 75,000-mol wt polypeptides. Monospecific antisera against p30, p15, p12, and p10 recognized polypeptides of mol wt 65,000, 75,000, 80,000 and 200,000, indicating that each shared antigenic determinants with all of these gag proteins. Using the appropriate authentic RLV precursor polypeptides as standards, comparative tryptic maps were performed with the ^{3}H-tyrosine or ^{35}S-methionine-labeled in vitro-synthesized 65,000- and 200,000-mol wt polypeptides. The former was found to be identical to Pr65-gag, a 65,000-mol wt RLV gag protein precursor obtained from infected cells by immunoprecipitation and gel electrophoresis. The second polypeptide was found to contain methionine-labeled tryptic peptides characteristic of RLV reverse transcriptase (pol) and p30. (44 refs)

78-5203 **Reverse Transcriptase-associated RNase H Activity: II. Inhibition by Natural and Synthetic RNA.** (Eng) Marcus, S. L. (Memorial Sloan-Kettering Cancer Center, New York, NY, 10021); Smith, S. W.; Modak, M. J. *J Virol* 27(3): 576-581; 1978.

The effect of exogenously added RNA molecules of natural and synthetic origin on the RNase H activities associated with purified avian myeloblastosis virus (AMV) and Rauscher murine leukemia virus (R-MuLV) DNA polymerases as well as on polymerase-independent RNase H activities was investigated. None of the polymerase-independent RNase H activities was inhibited by the addition of exogenous RNA, whereas those activities associated with R-MuLV and AMV DNA polymerases were strongly inhibited by RNA addition. It was also shown that the formation of duplex RNA completely abolished inhibitory activity and that various homopolymeric DNA's gave similar, if not identical, patterns of inhibition with R-MuLV DNA polymerase-associated RNase. However, polyguanylic acid was the only homopolymeric RNA that effectively inhibited this enzyme activity. An examination of RNA inhibition of the avian and murine oncoviral DNA polymerase-associated RNase H activities showed that they differed. Firstly, the relative efficiency of inhibition by various homopolymeric RNA molecules varied. Secondly, the RNase H activity associated with the AMV enzyme could be completely inhibited by increasing concentrations of naturally occurring RNA's, but that associat with the R-MuLV DNA polymerase was unaffected by t presence of such molecules at similar concentrations. Last R-MuLV DNA polymerase-associated RNase H activ could be inhibited by the addition of homopolymeric RN to an ongoing reaction, whereas similar additions did not fect the ongoing activity of the AMV polymerase-associat RNase H. (20 refs.)

78-5204 **A Combined Assay for the Rapid Prelimin Detection of Structural Retroviruses.** (Eng) lick, B. J. (David H. David Labs., Cancer Inst., Hahnema Medical Coll. and Hosp., 230 N. Broad St., Philadelphia, P 19102); Fuscaldo, A. A.; West, W.; Fuscaldo, K.; Brods I. *Cancer Lett* 4(3): 163-169; 1978.

Equilibrium gradients, RNA-dependent DNA polymer assays, and electron microscopy (EM) were used in a co bined assay for the rapid preliminary detection of intact troviruses in crude tissue preparations. The use of criti point drying as a preparative technique for EM is an integ part of this assay because it combines many of the advanta of thin sectioning and negative staining, but few of their li tations. Positive combined assays of platelets from prel kemic patients corresponded with their karyotypic abn malities. Reconstruction experiments with Rausch leukemia virus added to buffer or disrupted mouse spl demonstrated the ease of detecting $\geq 10^{9}$ particles/g cru tissue; however, 10^{8} particles or less were not detectable. T presence of added protein or other components of spleen sue appeared to enhance viral stability or affinity to the E grid. In unpublished results, platelets from patients w chronic myelogenous leukemia demonstrated the presence reverse transcriptase without visible particles. These findi indicate that intact particles may be present in some prel kemic states but only viral information and/or subunits main in most leukemic states. (18 refs)

78-5205 **Type-specific Radioimmunoassays for the gp7 of Mink Cell Focus-inducing Murine Leuken Viruses: Expression of a Cross-reacting Antigen in Cells fected with the Friend Strain of the Spleen Focus-formi Virus.** (Eng) Ruscetti, S. (Lab. Tumor Virus Genetics, NC Bethesda, MD, 20014); Linemeyer, D.; Feild, J.; Troxler, I Scolnick, E. *J Exp Med* 148(3): 654-663; 1978.

The gp70 of a helper-independent strain of a Friend mink c focus-inducing (MCF) virus, Fr-MCF-1, was isolated a used in a radioimmunoassay to detect any immunologi determinant(s) of the gp70s of MFC viruses derived fr Friend murine leukemia virus (F-MuLV), Moloney MuL and AKR-MuLV. Previous biochemical and biological st dies showed that Fr-MCF-1 is an envelope gene recombina between F-MuLV and a mouse xenotropic virus. The i munoassay utilized ^{125}I-Fr-MCF-1 gp70 and antiserum p

ared against an MCF strain of Moloney C-type virus. The MCF determinant(s) was not detected in the ecotropic parents of each of these MCF viruses, nor in helper-independent murine xenotropic viruses derived from Swiss or BALB/c mice. A protein partially cross-reactive with the MCF gp70 determinant(s) was detected in a replicating xenotropic virus derived from New Zealand Black mice. The MCF gp70-specific immunoassay could also detect a cross-reacting gene product coded for by the Friend strain of spleen focus-forming virus (SFFV) in rat fibroblasts nonproductively infected with SFFV. These findings support earlier molecular hybridization studies, which indicated that the genome of SFFV contains genetic information derived from both F-MuLV and xenotropic virus and that the xenotropic-related sequences in SFFV are highly related to those found in MCF murine C-type viruses. (14 refs.)

78-5206 **Helper-independent Mink Cell Focus-inducing Strains of Friend Murine Type-C Virus: Potential Relationship to the Origin of Replication-defective Spleen Focus-forming Virus.** (Eng) Troxler, D. H. (Lab. Tumor Virus Genetics, NCI, Bethesda, MD, 20014); Yuan, E.; Linemeyer, D.; Ruscetti, S.; Scolnick, E. M. *J Exp Med* 148(3): 639-653; 1978.

Cloned ecotropic Friend murine leukemia virus (F-MuLV) was inoculated into newborn NIH Swiss mice and the MuLV isolated from the preleukemic and leukemic spleens was used to study the relationship between the Friend erythroleukemia system and the AKR thymic leukemia system. Two helper-independent mink cell focus-inducing (MCF) strains of F-MuLV were isolated and shown by host range, interference pattern, and tryptic peptide analysis of the MuLV gp70s to be *env* gene recombinants between an ecotropic virus (F-MuLV) and a mouse xenotropic virus. Furthermore, RNA from the Friend MCF viruses hybridized completely to complementary DNA of spleen focus-forming virus (SFFV), a probe that detects that portion of SFFV not derived from F-MuLV. The ability to isolate replicating MCF viruses derived from F-MuLV strengthens the parallels between the Friend erythroleukemia system and the AKR thymic leukemia system. The potential relationship of helper-independent *env* gene recombinants between F-MuLV and xenotropic virus to the highly leukemogenic SFFV is discussed. (31 refs.)

78-5207 **An Analysis of the Role of Lymphatic Leukaemia Virus in the Immunodepression Exerted by Friend Complex in Leukaemia-resistant C57BL/6 Mice.** (Eng) Bendinelli, M. (Inst. Microbiology, Univ. Pisa, 56100 Pisa, Italy); Campa, M.; Toniolo, A.; Garzelli, C. *J Gen Virol* 39(2): 243-251; 1978.

The transient depression in the ability of leukemia-resistant C57BL/6 mice to develop IgM and IgG antibody-producing cells to sheep RBC following inoculation with the Friend leukemia complex (FLC) was investigated. Analysis of the lymphatic leukemia virus (LLV) component of FLC indicated that it was not capable of producing the same amount of immunodepression as the entire FLC. Mice inoculated with the Rowson-Parr isolate of LLV (RP-LLV) at various times before immunization constantly developed normal plaque-forming cell responses to sheep RBC. Following inoculation with the anemia-inducing strain of FLC from which RP-LLV was originally obtained, they exhibited a suppression of this response. A different isolate of LLV also failed to depress the plaque-forming cell responsiveness of C57BL/6 mice. Thus, the immunodepression cannot be attributed solely to the LLV component of FLC. This conclusion was also supported by evidence obtained from examining the replication of FLC and LLV, the antibody response to *Escherichia coli* lipopolysaccharide, and the ability of syngeneic macrophages administered together with the antigen to restore the response to sheep RBC. The mechanisms whereby FLC and its LLV component immunodepress are therefore partially different. (29 refs)

78-5208 **Analysis of Translational Products of Friend Strain of Spleen Focus-forming Virus.** (Eng) Barbacid, M. (Lab. Cellular and Molecular Biology, NCI, Bethesda, MD, 20014); Troxler, D. H.; Scolnick, E. M.; Aaronson, S. A. *J Virol* 27(3): 826-830; 1978.

Normal rat kidney (NRK) cells nonproductively infected with the Friend strain of spleen focus-forming virus (SFFV) were analyzed for the presence of murine leukemia virus (MuLV)-specific C-type viral proteins. SFFV was found to code for the p15 and p12 proteins of Friend-MuLV, as determined by immunological typing of their antigenic determinants. Molecular size analysis of the p15 and p12 proteins in SFFV nonproductively infected NRK cells indicated that these proteins are translated as parts of polyprotein molecules. The apparent mol wts of the polypeptides bearing p12 antigenic determinants revealed the presence of translational products of the SFFV genome that could not be accounted for by known C-type virus helper structural proteins. (29 refs)

78-5209 **Elimination of Infectious MuLV and Related Disease in LC Wild Mice by Selective Breeding.** (Eng.) Gardner, M. B. (Dept. Pathology, Univ. Southern California Sch. Medicine, Los Angeles, CA, 90032); Dougherty, M. F.; Casagrande, J.; Estes, J. D. *In: Advances in Comparative Leukemia Research 1977. Proceedings of the VIIIth International Symposium on Comparative Research on Leukemia and Related Diseases, held in Amsterdam, The Netherlands on 22-26 August, 1977.* Bentvelzen, P.; Hilgers, J.; Yohn, D. S., eds. (New York: Elsevier/North Holland Biomedical Press): 503 pp.; 88-89; 1978.

Infectious murine leukemia virus was eliminated from lym-

phoma/paralysis-prone LC wild mice by the selective breeding of nonviremic LC mothers. When the LC mothers were viremic, regardless of the serum virus status of the LC fathers, 92/115 of the F_1 progeny were viremic at 2 mo of age. When the LC mothers were nonviremic, only 2/172 of the progeny were viremic; all 114 of these progeny tested remained nonviremic to 9 mo of age. (6 refs)

78-5210 **Nearest-Neighbor Interactions of the Major RNA Tumor Virus Glycoprotein on Murine Cell Surfaces.** (Eng) Takemoto, L. J. (Dept. Microbiology, Univ. California, Los Angeles, CA, 90024); Fox, C. F.; Jensen, F. C.; Elder, J. H.; Lerner, R. A. *Proc Natl Acad Sci USA* 75(8): 3644-3648; 1978.

Chemical cross-linking was used in conjunction with immunoadsorption to probe for evidence of nearest-neighbor interactions of gp70 molecules, the major envelope constituent of C-type RNA viruses, on the surfaces of non-virus-producing [endogenous murine leukemia virus (MuLV)] murine cells. Radiolabeled gp70 molecules in LM fibroblast cells, B6 lymphocytes, and EL-4 lymphoma cells were linked to a protein of approx 15,000 daltons via native disulfide bonding. Prior treatment of the cells with the reversible, bifunctional, cross-linking reagent dimethyl-3,3′-dithiobispropionimidate, followed by immunoadsorption and two-dimensional diagonal electrophoresis, revealed apparent homodimers and homotrimbers of the 85,000-dalton complex. Identical treatment of purified type C RNA tumor virus from murine cells also revealed homodimeric and homotrimeric species, demonstrating similar self-associating tendencies of this glycoprotein in both intact virus and the plasma membranes of nonproducing murine cells. One cross-linked product consistently detected on the surfaces of murine cells was not present after cross-linking of a representative strain of MuLV. (49 refs.)

78-5211 **Distinguishable Biologic Effects of RNA Type-C Murine Leukemia and Sarcoma Viruses in Long-Term Bone Marrow Culture (Meeting Abstract).** (Eng) Greenberger, J. (Joint Center Radiation, Sidney Farber Cancer Inst., Boston, MA); Davisson, P.; Gans, P. *J Reticuloendothel Soc* 23(6): 36i; 1978. (no refs)

78-5212 **Induction of Endogenous Mouse Type C Virus (Meeting Abstract).** (Eng) Hellman, K. B. (George Washington Univ., Washington, DC, 20006). *Diss Abstr Int B* 39(1): 68B-69B; 1978. (no refs)

78-5213 **Two Different Murine Sarcoma Virus Isolates Have Homologous Genome Sequences: Implication for Their Origin.** (Eng) Deng, C. (Div. Chemistry and Chemical Engineering, California Inst. Technology, Pasadena, CA, 91125); Wimmer, E. *Virology* 89(1): 309-313; 1978

The RNase T1-resistant oligonucleotide fingerprints of the Moloney murine sarcoma virus clone 124 (MSV-214) and MSV clone 1712 were compared. Fingerprint comparison indicated that the RNA genomes of MSV-124 and MSV-1712 shared at least 14 large oligonucleotides, suggesting that the viruses are closely related. In view of this relationship, the hypothesis that MSV-1712 arose by recombination/deletion events of M4-MLV with mouse cellular DNA should be reconsidered. (16 refs.)

78-5214 **Heteroduplex Analysis of the Nonhomology Region Between Moloney MuLV and the Dual Host Range Derivative HIX Virus.** (Eng) Donoghue, D. J. (Dept. Biology, Massachusetts Inst. Technology, Cambridge, MA, 02139); Rothenberg, E.; Hopkins, N.; Baltimore, D. Sharp, P. A. *Cell* 14(4): 959-970; 1978.

The location of the glycoprotein coding sequences of the dual host range virus HIX was investigated by heteroduplex analysis. This virus was previously characterized as an envelope gene recombinant between Moloney murine leukemia virus (Mo-MuLV) and an unidentified xenotropic murine leukemia virus. Using long reverse transcripts of Mo-MuLV, a region of nonhomology was mapped by electron microscopic analysis of heteroduplexes formed with HIX 35S virion RNA. In this nonhomology region, the Mo-MuLV complementary DNA (cDNA) strand measured approx 900 nucleotides, mapping between 1.6 and 2.5 kilobases from the 3′ end. In a previous study, hybridization of Mo-MuLV 21S RNA with Mo-MuLV cDNA resulted in the formation of different heteroduplex structures diagnostic of a noncontiguously coded leader sequence at the 5′ end of the 21S RNA. Following hybridization of poly(A)+ HIX 21S RNA with 8.2-kilobase Mo-MuLV cDNA, analogous heteroduplex structures were observed exhibiting the Mo-MuLV:HIX substitution loop in the DNA:RNA segment of the molecules. This analysis permitted more precise mapping of the nonhomology region with respect to the splice point in the 21S presumptive glycoprotein messenger RNA. The mapping of this nonhomology region in HIX virus provides an internal visual marker for the 3′ end of the genome. (33 refs.)

78-5215 **High Frequency of Aberrant Expression of Moloney Murine Leukemia Virus in Clonal Infections.** (Eng) Shields, A. (Dept. Biology, Massachusetts Inst. Technology, Cambridge, MA, 02139); Witte, O. N.; Rothenberg, E.; Baltimore, D. *Cell* 14(3): 601-609; 1978.

The clonal progeny of a culture of NIH/3T3 cells infected with Moloney murine leukemia virus (M-MuLV) were studied for production of infectious virus, antigens of the virus,

nd noninfectious particles. There was approx one defective nfected clone for every two normal productive infected lones. One clone produced virus with altered plaque mor-hology, but others failed to produce particles able to make laques on XC cells. Two clones made particles lacking re-erse transcriptase, and they did not synthesize the reverse ranscriptase precursor Pr180-*gag-pol*. One clone (M23) ıcked both detectable glycoprotein and reverse transcrip-ıse. Despite these defects, all clones released particles with -type morphology, suggesting that *gag* gene function alone ıay be sufficient for particle production. The monomer NA's resulting from the denaturation of 70S RNA from all lones but M23 were electrophoretically indistinguishable om the RNA isolated from the producer line. All particles ontained viral RNA of 60S-70S that was composed of the ormal 35S size subunits except for M23, which had a dele-on in the viral genome of approx 1,000-1,500 nucleotides. variety of defective clones were also isolated from normal it kidney cells infected with M-MuLV. Apparently, the luLV genome is often mutated by spontaneous processes enerating a wide range of phenotypes. (36 refs.)

8-5216 **A Competition Immunoassay for Characterizing the Reverse Transcriptase of Mammalian RNA umor Viruses.** (Eng) Panet, A. (Dept. Virology, Hebrew Iniv., Hadassah Medical Sch., Jerusalem, Israel); Kra-oz, Z. *irology* 89(1): 95-101; 1978.

simple and rapid competition enzyme immunoassay for the everse transcriptase (RT) of mammalian RNA tumor iruses is described. The assay is based on competition be-veen an enzymatically active RT probe and a sample tested or RT antigen on a limited amount of monospecific anti-ody. The extent of competition is determined from the esidual DNA polymerase activity left in the probe. Any RT ctivity in the test sample that could interfere with the en-ymatic assay is inhibited irreversibly by pretreatment with I-ethylmaleimide. Thus, increasing amounts of test antigen eutralize more antibodies and restore more of the RT probe ctivity. The type, group, and interspecies antigenic determi-ants in the RT of mammalian RNA tumor viruses were esolved using the competition assay. The assay was also use-il for quantitating the amount of RT present in virions. Ap-lication of this procedure to Moloney murine leukemia virus evealed that RT comprised 2.5% of the total viral proteins. 11 refs.)

8-5217 **Genome Organization of RNA Tumor Viruses. I. In Vitro Synthesis of Full-Genome-Length ingle-stranded and Double-stranded Viral DNA Tran-ripts.** (Eng) Verma, I. M. (Tumor Virology Lab., Salk Inst., an Diego, CA, 92112). *J Virol* 26(3): 615-629; 1978.

he synthesis of large complementary DNA (cDNA) tran-ripts from avian myeloblastosis virus (AMV), a cloned iso-late of Moloney murine leukemia virus (M-MuLV), and Moloney murine sarcoma virus (M-MSV) were studied. The longest cDNA transcripts synthesized using AMV, M-MuLV, and M-MSV (clone 124) were 7, 9, and 6.5 kilobases (kb), respectively. Double-stranded DNA could also be synthesized in vitro, but the second strand had an av size of only 0.8 to 1.2 kb. Two methods were used to synthesize double-stranded M-MuLV: (1) the 3′ end of the minus strand was extended by the addition of 50 to 100 deoxyAMP residues using terminal deoxynucleotidyl transferase, and the plus strands were synthesized using the (dA)n-tailed cDNA transcripts as templates, an oligomer of deoxythymidine (dT) as primer, and *Escherichia coli* DNA polymerase; and (2) DNase-digested calf thymus DNA was used to prime the synthesis of plus strands on long cDNA with *E. coli* DNA polymerase I. Regardless of the size of the parent cDNA transcripts, both methods were capable of synthesizing double-stranded viral DNA. The plus strand of DNA synthesized by oligo(dT) primer sedimented heterogeneously with an av size of 5 to 6 kb, whereas the plus strands synthesized by calf thymus DNA primer appeared to be no longer than 0.3 to 0.4 kb. It was possible to synthesize double-stranded DNA without primer, but the plus strand of DNA was covalently linked to the parent strand. (60 refs)

78-5218 **Generation of New Mouse Sarcoma Viruses in Cell Culture.** (Eng) Rapp, U. R. (Lab. Viral Carcinogenesis, NCI, NIH, Bethesda, MD, 20014); Todaro, G. J. *Science* 201(4358): 821-824; 1978.

Endogenous non-tumor-producing C-type viruses from C3H mice that replicated in transformed mouse fibroblast cell lines generated variants that could directly transform cells in culture. The variants also induced rapid formation of undifferentiated sarcomas in 100% of newborn NIH Swiss mice inoculated ip with 50 μl of culture fluid. The foci that were induced by the new variants in cultured cells initially showed signs of only minimal transformation when compared with foci induced by standard laboratory strains of murine sarcoma virus. Also, the morphological effects that accompanied the adaptation to high-titer growth in a particular cell line were transient; immediate selection of virus released from these areas of transient transformation was needed in order to isolate the more stable, solid-tumor-inducing variant. The data show that variants of endogenous C-type virus that contain transforming genes (oncogenes) can arise during spread of the endogenous virus in fibroblast lines in vitro as well as in susceptible tissues in vivo. (26 refs.)

78-5219 **'Nonproductive' Mouse Sarcoma Virus Transformed Gorilla Cells which Contain Noninfectious Type C Virus Particles.** (Eng) Rhim, J. S. (Microbiological Associates, Inc., Bethesda, MD, 20016); Park, D. K.; Vernon, M. L. *Proc Soc Exp Biol Med* 158(3): 304-309; 1978.

Gorilla spleen cells were readily transformed morphologically in vitro by Kirsten murine sarcoma virus (Ki-MSV) and the MSV pseudotype of baboon placenta virus (MSV-BP). The Ki-MSV stock used was a rat cell-grown virus. MSV-BP was produced in human sarcoma-positive, leukemia-negative cells by cocultivation with a baboon virus-releasing human osteosarcoma line. The morphology of the Ki-MSV- and MSV-BP-transformed foci was similar. However, cells transformed by MSV-BP were producers, but the Ki-MSV-transformed cells were nonproducers (NP). These NP cells were induced by simple infection of gorilla cells with Ki-MSV. The NP cells did not release any infectious virus or murine leukemia virus group-specific antigen, but they did contain a rescuable MSV genome and noninfectious C-type particles with a buoyant density of 1.16 g/ml. Evidence is presented to show that the NP gorilla cells represent a new class of transformants; that is, gorilla NP cells containing noninfectious C-type virus without viral antigen. Attempts to rescue the genome of the focus-forming virus from gorilla NP cells by 5-bromodeoxyuridine yielded negative results. (23 refs.)

78-5220 **Growth Factors from Murine Sarcoma Virus-transformed Cells.** (Eng) De Larco, J. E. (Lab. Viral Carcinogenesis, NCI, NIH, Bethesda, MD, 20014); Todaro, G. J. *Proc Natl Acad Sci USA* 75(8): 4001-4005; 1978.

The partial purification of a family of growth-stimulating polypeptides, sarcoma growth factors, from the supernatant fluids of Moloney murine sarcoma virus (MuSV)-transformed mouse 3T3 cells is described. These factors stimulate cells to divide in monolayer cultures and also to form colonies that grow progressively in soft agar. Three major peaks of activity were seen with apparent mol wts of 25,000, 12,000, and 7,000 daltons. The sarcoma growth factors were heat-stable, trypsin-sensitive, and active in nanogram quantities when tested for growth stimulation of untransformed rat and mouse fibroblasts. All three molecular species were also capable of competing for membrane epidermal growth factor (EGF) receptors when tested with ^{125}I-labeled EGF. However, they differed from mouse EGF in their mol wt, their inability to react with anti-EGF antibodies, and in their ability to convert cells to anchorage-independent (agar) growth. It is concluded that these sarcoma growth factors are a new class of polypeptide tropic factors that confer properties associated with the transformed phenotype on fibroblasts in vitro. (20 refs.)

78-5221 **Particles from Mouse Melanoma B16 Containing Reverse Transcriptase and 70 S RNA Related to Human Melanoma Cytoplasmic RNA.** (Eng) Hehlmann, R. (Medizinische Poliklinik, Ludwig-Maximilians-Universitat, Pettenkoferstrasse 8a, D-8000 Munich 2, W. Germany); Balda, B. R.; Spiegelman, S. *Arch Dermatol Res* 262(2): 157-165; 1978.

The viruslike particles in B16 mouse melanomas were char terized. Material from a spontaneous melanoma was de ty-fractionated, and the viral-enriched fractions (density 1 g/cm^3) were used for an endogenous reverse transcript reaction followed by glycerol sedimentation analysis of deproteinized nucleic acids. A portion of the ^{3}H-DNA se mented in discrete 70S peaks in the gradients. After RN digestion of the 70S-^{3}H-DNA, all the radioactivity was fou in the low-mol-wt region of the gradient, showing that ^{3}H-DNA was complexed to a high-mol-wt DNA. Thus, particles in the B16 melanoma contained a high-mol-wt RNA associated with reverse transcriptase and possessed density characteristics of RNA tumor viruses. The ^{3}H-DN synthesized by the particles hybridized back to its templ RNA; no hybrids were observed with mouse mammary mor virus or avian myeloblastosis virus 70S RNA. T ^{3}H-DNA also showed homology to RNA isolated from hamster melanoma and from three human malignant melar mas: > 7% hybridized to hamster melanoma RNA and to 5.7% hybridized to the human melanoma RNA. (30 re

78-5222 **Mammary Tumor Virus DNA: A Glucoc ticoid-responsive Transposable Element.** (E Yamamoto, K. R. (Dept. Biochemistry and Biophysi Univ. California, San Francisco, CA, 94143); Stallcup, M. Ring, J.; Ringold, G. M. *Cold Spring Harbor Symp Qua Biol* 42(part 2): 625-638; 1978.

Studies of the effects of dexamethasone on the expression chromosomal sequences coding for mammary tumor vi (MTV) are described, along with evidence consistent with t idea that the MTV DNA sequence is a glucocorticoid-respo sive transposable genetic element. When viral DNA was p sent in the genomes of a variety of mammalian cell types a was transcribed at a basal level, dexamethasone appeared stimulate viral RNA production selectively. Evidence i dicating that the stimulation of viral RNA production is t result of an immediate shift to a new rate of transcription the MTV genes is reviewed. Preliminary results indicate th RNA synthesis under cell-free conditions appears to refle faithfully these different efficiencies of specific gene transcri tion. In experiments with MTV-infected HTC cells, the e tent of viral gene expression and hormone responsiveness va ied from clone to clone. Furthermore, infected clones we altered in the expression of a few specific genes. Unintegrat viral DNA was produced in these cells, perhaps via rever transcription, but it probably was not extensively transcrib into RNA. (93 refs.)

78-5223 **Genetic Transmission of Mammary Tumou Virus in the DBAf Mouse Strain.** (Eng) Verst aeten, A. A. (Div. Genetics, Antoni van Leeuwenhoekhui Netherlands Cancer Inst., Amsterdam, Netherlands); va Nie, R. *Int J Cancer* 21(4): 473-475; 1978.

Mouse mammary tumor virus (MTV) antigens were demonstrable by radioimmunoassay (RIA) in milk samples from individual DBAf mice and in samples from (female BALB/c x male DBAf)F_1 mice. Some samples collected during the first lactation periods were virus-negative but all samples of later lactation periods were virus-positive. Milk samples from 42/75 mice of the [female BALB/c x male(female BALB/c x male DBAf)]Bc I population were virus-positive. In the [BALB/c x (BALB/c x DBAfi) x BALB/c)Bc II population two groups were distinguished. In the first group, the progeny of virus-positive Bc I mothers, 37/62 mice had detectable levels of viral antigen in the milk. None of the 43 samples from mice of the second group, derived from MTV-negative Bc I females, were virus-positive. Statistical analysis of the Bc I and Bc II data revealed that the segregation ratios did not deviate significantly from 1:1 ratios, which suggests that one dominant gene of DBAf mice controls the expression of viral antigens in the milk. DBAf mice have the non-agouti/-brown/dilute coat color phenotype (a, b, d) and BALB/c mice the albino phenotype (alleles b, c). When the RIA data were grouped according to the coat color phenotype, a linkage relationship was observed between the absence of viral antigens in the milk and the c allele of the albino locus on chromosome 7 (recombination percentage: 20). (17 refs)

78-5224 **Dependent and Autonomous Phases During Leukemogenesis.** (Eng) Haran-Ghera, N. (Dept. Chemical Immunology, Weizmann Inst. Science, Rehovot, Israel). *Leuk Res* 2(1): 11-21; 1978.

The induction of leukemia in C57BL/6 mice by intrathymic injection of radiation leukemia virus variants that induce a high leukemia incidence (A-RadLV, 80%-100% incidence) or a low incidence (D-RadLV, 0%-20%) was investigated. Some mice were treated with D-RadLV plus, 3 days later, 400 R of whole-body x-radiation, which also yields a high leukemia incidence (70%-100%). The occurrence of preleukemic (PL) cells in the thymus (Th) and bone marrow (BM) was analyzed by cell transfer-genotype analysis. Samples of BM, Th, and whole blood, collected after 10-80 days from the treated mice, were injected iv into normal or irradiated syngeneic or (BALB/c x C57BL/6)F_1 hybrids. The earliest (10 days) and highest incidence of PL cells was found in the BM of mice treated with D-RadLV alone. In contrast, in mice treated with A-RadLV or D-RadLV + radiation, PL cells were identified approx 30 and 40 days after injection, respectively. The latent period of leukemia development following transfer of BM cells from D-RadLV-treated donors was always delayed (100-125 days), irrespective of the time between virus injection and BM sampling. The ability of D-RadLV to induce a high incidence of PL cells indicates that a leukemogenic agent might exert a transformation effect without necessarily providing the proliferative capacity that would ultimately contribute to autonomous tumor development. An intact Th was required for the initiation of PL cell proliferation, which consisted of two phases, dependent and autonomous. In the former, the preferential growth of PL cells in pretreated hosts depended on specific host environments (presence of Th, host irradiation, availability of specific lymphocyte populations). Ultimately, following sustained proliferation, the dependent PL cells underwent changes, with the emergence of autonomous clones whose proliferation was independent of host environment. The high or low potential of leukemogenic agents might be related to their capacity to induce dependent or autonomous transformed cells. Possible mechanisms involved in the transition from dependence to autonomy are given. (16 refs.)

78-5225 **Characterization by Molecular Hybridization of Two Viral Populations Derived from a Radiation Leukemia Virus.** (Eng) Janowski, M. (Departement de Radiobiologie, Centre d'Etude de l'Energie Nucleaire, B-2400 Mol, Belgium); Astier, T.; Guillemain, B.; Baugnet-Mahieu, L.; Duplan, J. F.; Maisin, J. R. *Cancer Res* 38(10): 3487-3493; 1978.

Two leukemogenic viral populations were derived from a radiation leukemia virus of the C57BL mouse and characterized. One (FB), in which only B-tropic virus could be detected, was obtained in vivo by serial passage of a cell-free extract in newborn rats. The second (3C), a complex containing at least B-tropic and xenotropic viruses, was produced in vitro by a permanent cell line (13-3C) established from the spleen of a virus-infected C57BL mouse. In molecular hybridization experiments, the 70S RNA of Gross leukemia virus hybridized 96% and 78% of FB and 3C radioactive complementary DNA's, respectively, with the duplexes formed having a relatively high thermal stability. In contrast, the 70S RNA of Rauscher leukemia virus hybridized 23% and 20% of the FB and 3C DNA probes, respectively, and the duplexes had low thermal stability. The rat-grown FB virions exhibited 50% genome homology with the viruses produced in vitro on the 13-3C cells. Finally, hybridizing the FB and 3C probes with normal or leukemic mouse spleen DNA's resulted in 89% to 100% homology. The rat-grown virions did not appear to contain detectable rat cellular DNA sequences, but about 20 complete copies of their nucleotide sequences were detected in covalent linkage with FB-infected rat spleen DNA. These findings strongly support the endogenous murine origin of the investigated virions. (27 refs.)

78-5226 **Double-stranded DNA Synthesized by RD-114 Virion DNA Polymerase.** (Eng) Yamazaki, H. (Dept. Molecular Biology, Cancer Res. Inst., Sapporo Medical Coll., Sapporo 060, Japan); Fujinaga, K. *Tumor Res (Sapporo)* 12: 29-36; 1977.

The double-stranded DNA (dsDNA) of RD-114 virus (an endogenous C-type feline virus) was synthesized by RD-114 virion DNA polymerase and used as a probe to investigate RD-114 virus-related DNA sequences in human cells. According to the reassociation kinetics of purifed ^{3}H-dsDNA,

the dsDNA was heterogeneous. DNA-DNA reassociation was used to separate the dsDNA into three fractions: a rapidly reassociating fraction (RR), and two slowly reassociating fractions (SR-1 and SR-2). The nucleotide complex of the RR fraction weighed 1.32 x 10^6 daltons (13.1% of the viral genome), and that of the SR-1 fraction weighed 3.34 x 10^6 daltons (33.1% of the viral genome). The size of nucleotide complex of SR-2 fraction could not be determined because of the heterogeneity of this fraction. Addition of human cell DNA (from a Burkitt's lymphoma line P3HR-1, peripheral blood of patients with acute myelogenous leukemia, and a rhabdomyosarcoma line RD) did not significantly accelerate the reassociation of the RR fraction. However, RD cell DNA appreciably accelerated the reassociation of SR-1 and SR-2, which suggests that RD-114 virus-related sequences were present in RD cells. Hybridization experiments with single-stranded DNA (ssDNA), which represented most of the viral genome sequences, and human DNA showed that only a small percentage of the ssDNA hybridized with human DNA. In addition, the thermal denaturation curves were broad. These findings indicate that few sequences specifically related to RD-114 DNA were present in human cells. (14 refs.)

78-5227 **Potentiation of the Neutralization of Feline Leukaemia Virus in Hypotonic Medium.** (Eng) Russell, P. H. (ICRF Tumour Immunology Unit, Dept. Zoology, Univ. Coll. London, Gower St., London WC1E 6BT, England). *J Gen Virol* 40(2): 373-378; 1978.

The neutralization of feline leukemia virus was found to be enhanced by performing the reaction in hypotonic medium. Absorption of neutralizing antibody by virus-specific antigens was also more sensitive in this medium. In one experiment, the serum titer of the virus was increased 30 times and the infectivity was decreased fivefold. (10 refs.)

78-5228 **Production of Antibodies against Feline Leukemia and Sarcoma Viruses and the Feline Oncovirus-associated Cell Membrane Antigen in Strain 2 Guinea Pigs.** (Eng) Log, T. (NCI, NIH, Bethesda, MD, 20014); Chang, S. S.; Sarma, P. S. *Virology* 89(1): 300-305; 1978.

Cloned cell lines of a guinea pig tumor induced by the Snyder-Theilen strain of feline sarcoma virus with feline leukemia virus subgroup C as helper [ST-FeSV (FeLV-C)] were established to study the host-virus relationship in an inbred laboratory animal strain. The cell line released high ST-FeSV titers (FeLV-C) (10^3-10^4 focus-forming units/0.2 ml) and 1 log excess of FeLV-C. In vivo studies with one cell line, GPTC $C1_1$, indicated that as little as 100 cells could induce tumors in weanling strain-2 guinea pigs following sc administration. The tumors grew progressively and killed the animals within 23 days. Sera from tumor-bearing guinea pigs contained antibodies to FeLV group-specific antigen, FeLV-C virus envelope antigen, and feline oncovirus-associated ce membrane antigen. Absorption tests with the appropriate a tigens suggested that the three antibodies were distinct. (2 refs.)

78-5229 **Studies on a Possible Viral Aetiology of Canin Lymphosarcoma and Mammary Tumour (Meeting Abstract).** (Eng) Armstrong, S. J. (Dept. Clinica Veterinary Medicine, New Addenbrooks Hosp., Cambridg England); Nunes de Souza, P.; Wreghitt, T. G.; Nagingto J.; Mahy, B. W.; Owen, L. N. *Br J Cancer* 38(1): 175; 197 (1 ref)

78-5230 **Distribution of Bovine Leukemia Virus Provir DNA Sequences in Tissues of Animals with E zootic Bovine Leukosis.** (Eng) Kettmann, R. (Departemen de Biologie Moleculaire, Universite Libre de Bruxelles, Bu sels, Belgium); Burny, A.; Cleuter, Y.; Ghysdael, J.; Mam merickx, M. *Leuk Res* 2(1): 23-32; 1978.

Normal and malignant tissues of bovine, ovine, porcine, an human origin were investigated for the presence of bovin leukemia virus (BLV) proviral DNA sequences using a BL ^{3}H-thymidine-labeled, single-stranded, complementary DN (cDNA) probe synthesized on purified BLV 60S-70S RN as template by avian myeloblastosis virus. The malignant tis sues were obtained from cattle and sheep experimentally in fected with BLV, field cases of enzootic bovine leukosi (EBL, sporadic cases), a lymphoid tumor from a leukemi pig, and human leukemias and sarcomas. After recyclin against normal bovine DNA, the probe hybridized with EB tumor DNA in sheep and cattle but not with normal bovin DNA. The highest hybridization levels were obtained wit tumorous lymph nodes (35%-38%). These results indicat that BLV is an exogenous RNA oncogenic virus and confir that EBL is an infectious disease. Proviral BLV sequence were also detected in buffy coat cells of animals with persist ent lymphocytosis (PL) and carrying antibodies to BLV bu without tumors (30%-45% hybridization). This result clear ly establishes that PL (without tumor formation) is most o the time, if not always, a subclinical form of EBL. In tu mor-bearers, the proviral sequences were found in buffy coa cells, in solid tumors (lymphosarcomas) and in organs infil trated with tumoral lymphoid cells but not in apparently nor mal organs. No hybridization above background was ob served with DNA's extracted from buffy coat cells an tumors from the sporadic forms of bovine leukosis, pig leu kemia, and the human cancers. Thus, BLV is probably un related to human cancers. (27 refs)

78-5231 **A Gene (*Bevi*) on Human Chromosome 6 Is an Integration Site for Baboon Type C DNA Provirus in Human Cells.** (Eng) Lemons, R. S. (Lab. Viral Car-

nogenesis, NCI, Bethesda, MD, 20014); Nash, W. G.; O'rien, S. J.; Benveniste, R. E.; Sherr, C. J. *Cell* 14(4): 95-1005; 1978.

n attempt was made to map genetically a putative integraon site for baboon endogenous C-type virus in humans using ie technique of somatic cell hybridization. Human VA-2 ells infected with baboon C-type virus were cloned and fused Syrian hamster cells, and 33 primary hybrid colonies were btained. These cells segregated human chromosomes and etained the complete hamster genome. Assays for C-type iral p30 antigen and reverse transcriptase were performed conjunction with analyses of 30 gene-enzyme systems epresenting 22 different human chromosomes. The results ndicated that a gene, *Bevi*, previously assigned to human hromosome 6, dominantly controls baboon C-type virus xpression in hybrid cells. Representative hybrid clones were tudied by nucleic acid hybridization techniques for the presnce of integrated proviral DNA using complementary H-DNA transcripts of the baboon viral RNA genome. For ach of 12 clones examined, there was a concordance between ie presence of human chromosome 6, the presence of baboon C-type proviral DNA sequences, and virus expression. Clones that segregated chromosome 6 (according to isozyme nd karyological analyses) lost detectable proviral DNA seuences and failed to produce virus. There was no syntenic ssociation between the replication of baboon virus and the resence of 21 other human chromosomes. It is concluded hat *Bevi* is a preferred integration site for the baboon C-type rovirus in the human genome. (47 refs.)

8-5232 **Susceptibility of Human Cultured Cells to Mason-Pfizer Monkey Virus.** (Eng) Ogura, H. Dept. Virology, Cancer Inst., Okayama Univ. Medical Sch., Okayama, Japan); Ocho, M.; Tanaka, T.; Oda, T. *Gann* 9(3): 413-415; 1978.

Cultures of the following seven types of human cells were noculated with Mason-Pfizer monkey virus (M-PMV) to ascertain which types are susceptible to this virus: fibroblasts rom whole embryo (HEC) and embryonic lung (HEL) cells, Detroit-551 embryonic skin cells, RSb cells (embryonic cells lually transformed by Rous sarcoma virus and simian virus 40), glial (KC) cells, and epithelioid carcinoma cells (HeLa nd HEp-2). The infected cultures were maintained routinely vith periodic transfers for 25 days and then examined elecron microscopically and by the KC syncytium assay. All of he cells produced M-PMV-like particles approx 100 nanomeers in diameter. Budding, extracellular, and intracytoplasmic particles resembling A-type particles were seen. None of he infected cells showed morphological changes. Mock-infected control cultures did not contain viruslike particles. Syncytium formation was observed at the second transfer of M-PMV-infected HEC, HEL, and Detroit-551 cells coculivated with KC cells, but not in HeLa, HEp-2, RSb, and KC cells, even at the fifth transfer. However, these syncytium-negative cells showed M-PMV under the electron microscope and in an infectivity assay of KC syncytium formation. The titers were 10^{-4} syncytium-forming unit/0.2 ml for HEC, HEL, and Detroit-551 cells; 10^{-3} for RSb and KC cells; and 10^{-1} for HeLa and HEp-2 cells. Thus, M-PMV propagated well in human fibroblastic cells and poorly in human epithelioid cells. (17 refs.)

78-5233 **Inhibition of Adenovirus Replication by 5,6-Dichloro-1-β-D-ribofuranosylbenzimidazole.** (Eng) Brotz, M. (Inst. Genetics, Univ. Cologne, Cologne, W. Germany); Doerfler, W.; Tamm, I. *Virology* 86(2): 516-529; 1978.

The halogenated benzimidazole derivative 5,6-dichloro-2-β-D-ribofuranosylbenzimidazole (DRB) reversibly inhibited the replication of human adenovirus type 2 (Ad2) and viral DNA in human KB cells. At 60 μM, DRB reversibly inhibited Ad2 replication in KB cells by > 99.9% when it was added at the time of infection and present throughout infection. Viral DNA replication was almost completely inhibited when the drug was added < 4 hr postinfection in concentrations between 50 and 150 μM. This inhibition affected all four size classes of viral DNA (> 100S, 50S-90S, 34S, and < 20S). The replication block was reversible upon withdrawal of the inhibitor. When DRB was administered at the time of max viral DNA replication, 16-18 hr postinfection, the inhibitor had no apparent effect on viral DNA synthesis. In the presence of 150 μM DRB, the synthesis of early virus-specific RNA in the nucleus was reduced by approx 90% and the appearance of virus-specific RNA sequences in the cytoplasm by > 95%, as demonstrated by DNA-RNA filter hybridization. Thus, the block in viral DNA replication is best explained by the inhibition of early virus-specific RNA synthesis. (36 refs)

78-5234 **Alterations in Surface Glycoproteins and Level of Sialyltransferase Activity of Human Embryo Kidney Cells Infected with Oncogenic Adenovirus Type 12.** (Eng) Aoi, Y. (Inst. Medical Science, Univ. Tokyo, Tokyo 108, Japan); Yokota, M. *Tohoku J Exp Med* 125(2): 177-183; 1978.

A comparative study of plasma membrane glycoproteins and microsomal sialyltransferase activity was conducted in cultures of human embryo kidney (HEK) cells and in HEK cells infected with wild-type human adenovirus type 12 (H12) or *Cyt* mutants of H12. The H12 mutants used were *Cyt*66 (highly tumorigenic) and *Cyt*31 (less tumorigenic). The sodium dodecyl sulfate-polyacrylamide gel electrophoretic patterns of HEK cells demonstrated major glycoproteins in fractions 10, 18, and 19. Cells infected with H12 synthesized fraction 10 glycoprotein but not that of fractions 18 and 19. Cells infected with the *Cyt* mutants did not produce fraction 10 glycoprotein. Investigations of microsomal sialy transferase indicated that the enzyme activity in H12-infected cells was increased by 230% over that seen in uninfected cells. The

level of sialyltransferase in *Cyt*66-infected cells was 1.23 times higher than that of *Cyt*31-infected cells. Thus, there was a positive correlation between sialyltransferase activity in the microsomes and tumorigenicity. (27 refs)

78-5235 **Are Oncogenic Human Adenoviruses Associated with Human Cancer? Analysis of Human Tumors for Adenovirus Transforming Gene Sequences.** (Eng) Green, M. (Inst. Molecular Virology, St. Louis Univ. Sch. Medicine, St. Louis, MO, 63110); Mackey, J. K. *In: Mechanisms of Carcinogenesis. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book B), 699 pp.; 1027-1042; 1977.

An adenovirus (Ad) etiology of human cancer was tested using sensitive Ad DNA probes to detect Ad DNA sequences in human tumors. Ad12 DNA and the Ad12 transforming restriction fragments (*Eco*RI-C fragment) were labeled in vitro to 10^7 to 4 x 10^8 cpm/μg by nick translation. Using Ad12-^{3}H-DNA as a probe, DNA or RNA from 18 normal gastrointestinal (GI) tissues and 34 tumors, including cancers of the colon, rectum, small intestine, and stomach, was analyzed under conditions that would detect 0.1 copy of the Ad12 genome per tumor cell. No hybridization was detected with DNA or RNA extracted from 57 GI tumors, indicating that Ad12 is not a major cause of human GI cancer. The *Eco*RI-C fragment hybridized 50%-60% with other Ad12 isolates and with Ad18 and Ad31 (members of oncogenic group A), but not with 28 other human Ad serotypes. Thus, other group A members probably are also not involved in human GI cancer. No Ad12 DNA sequences were detected in 22 lung tumors, and no Ad12 *Eco*RI-C sequences were detected in 57 lung tumor DNA or RNA specimens. Similar experiments in which DNA or RNA from 55 GI tumors and 53 lung tumors was analyzed for the presence of sequences homologous to the transforming Group C Ad2 *Hind*III-G restriction fragment excluded the presence of less than one copy of 1% of the Ad2 genome in these tumors. Since Ad2 *Hind*III-G sequences are also present in all group C Ad's, these data indicate that group C Ad's do not cause 98% of human GI and lung tumors. (24 refs)

78-5236 **Target Cells of Adenovirus Type 12 in Brain Cell Cultures (Meeting Abstract).** (Eng) Ogawa, K. (Okayama Univ. Medical Sch., Okayama, Japan); Sonobe, H. *J Neuropathol Exp Neurol* 37(5): 667; 1978. (no refs)

78-5237 **Patterns of Integration of Viral DNA Sequences in the Genomes of Adenovirus Type 12-Transformed Hamster Cells.** (Eng) Sutter, D. (Inst. Genetics, Univ. Cologne, Cologne, W. Germany); Westphal, M.; Doerfler, W. *Cell* 14(3): 569-585; 1978.

The patterns of integration of the viral genome were analyz in four hamster cell lines (HA12/7, T637, A2497-2, a A2497-3) transformed by adenovirus type 12 (Ad12). F each cell line, a distinct and specific pattern of integrated vi DNA sequences was observed for each restriction endon clease (*Bam* HI, *Bgl* II, *Eco* RI, *Hind* III, *Hpa* II, and *S* I) used. The distribution patterns of the viral sequences co plementary to the isolated *Eco* RI restriction endonucle fragments were also specific for each cell line. Some of t viral DNA molecules were fragmented prior to or duri integration. The *Eco* RI B, D, and E fragments, comprisi a contiguous segment from 0.17 to 0.62 fractional leng units of the viral DNA, remained intact during integrati in a portion of the viral DNA molecules. Although each c line carried multiple copies of Ad12 DNA, the viral DN sequences were concentrated in a small number of distin size classes of fragments. In the three cell lines tested (T63 A2497-2, and HA12/7), the integration pattern was stab over many generations and was identical in a number of ra domly isolated clones. The data support the hypothesis th at least a portion of the viral DNA sequences is integrat into repetitive sequences or else that the integrated viral s quences are amplified after integration. (33 refs.)

78-5238 **Transformation-specific Antigen Induced Oncogenic Human Adenovirus.** (Eng) Ledink N. (Dept. Biology, Univ. Akron, Akron, OH, 44325). *Natu* 274(5673): 812-813; 1978.

The human adenovirus type 12 (H12) transformation-specif protein(s) in H12-transformed cell lines was studied. 60,000-mol wt transformation-specific antigen in H12-tran formed rat 3Y1 cells was identified by immunoprecipitatio of ^{35}S-methionine-labeled polypeptides with serum fro H12-tumor-bearing hamsters. The expression of this antige was temperature-dependent in 3Y1 cells transformed by th temperature-sensitive H12 mutant *ts*401. The altered beha ior of the 60,000-mol wt protein observed in mutant infectio strongly suggests that it is the product of the 401 gene. Alte natively, the protein may be a cell-coded protein, induced b the 401 function, and its reduction under restrictive cond tions may reflect host cell alterations associated with a retur to the normal phenotype. (25 refs.)

78-5239 **Transformation of Marmoset Lymphocytes I Vitro with *Herpesvirus ateles*.** (Eng) Falk, I (Dept. Microbiology, Rush-Presbyterian-St. Luke's Medica Center, Chicago, IL, 60614); Johnson, D.; Deinhardt, F. *I J Cancer* 21(5): 652-657; 1978.

Continuous lymphoblastoid cell lines with T-lymphocyt cell-surface markers were established from marmoset cir culating lymphocytes transformed in vitro by *Herpesviru ateles* (HVA). Blood samples were obtained from wild-caugh cotton-topped (*Saguinus oedipus*), white-lipped (*S. fuscicollis*

S. nigricollis), and common (*Callithrix jacchus*) marmosets. Transformation was effected by cocultivating the lymphocytes with lethally x-irradiated HVA-producing lymphoblastoid cells (I) or by infecting them with cell-free virus (II). A total of 10/17 cotton-topped, 13/16 white-lipped, and 19/39 common marmoset lines were obtained 17-35 days after transformation method I was initiated; 2/4 cotton-topped marmoset lines were established 51-53 days after the start of method II. Attempts to transform squirrel monkey lymphocytes by method I were not successful. The association of HVA with each transformed culture was demonstrated by staining of antigen-positive cells in indirect fluorescent antibody tests and recovery of HVA after cocultivation of the transformed cells with permissive monolayer cells. Cells of most of the transformed cultures formed E (erythrocyte) rosettes, reacted with a specific anti-marmoset T-lymphocyte serum, and lacked surface immunoglobulin, properties identifying them as T cells. (22 refs)

78-5240 **Replication of Herpesviruses in Human Cells Transformed by Cytomegalovirus.** (Eng) Figueroa, M. E. (Dept. Microbiology, Milton S. Hershey Medical Center, Pennsylvania State Univ. Coll. Medicine, Hershey, PA, 17033); Geder, L.; Rapp, F. *J Gen Virol* 40(2): 391-398; 1978.

The replication of human cytomegalovirus (CMV) and herpes simplex virus (HSV) was studied in three human embryo cell lines (CMV-Mj-HEL-1, CMV-Mj-HEL-2, and CMV-Mj-HEL-2,T-1) transformed in vitro by human CMV. Growth studies revealed that these cells were completely resistant to infection by CMV strains AD169 and Mj and partially resistant to HSV types 1 and 2. Neither virus DNA nor virus proteins were synthesized in the transformed cells infected with CMV AD169. HSV production in CMV-transformed human embryo lung (HEL) cells was delayed when compared with the virus production in normal HEL cells, and spread of the cytopathic effect of HSV was slower in the transformed cells. The treatment of normal HEL cells with a crude extract of CMV-transformed HEL cells also resulted in inhibition of the spread of the cytopathic effect of HSV types 1 and 2. The inhibitory effect was not due to interferon, since vesicular stomatitis virus replication was not affected and several experiments showed that it was not due to mycoplasma. It is postulated that there are virus inhibitor molecules in CMV-transformed cells and that they are absent in normal HEL cells. (16 refs.)

78-5241 **Detection of Epstein-Barr Virus DNA in Anaplastic Carcinoma of the Nasopharynx and Other Tumors.** (Ger.) Wolf, H. (Max von Pettenkofer-Institut Hygiene, Munich, W. Germany). *Fortschr Med* 96(15): 832; 1978.

Epstein-Barr virus (EBV) DNA was found in anaplastic nasopharyngeal carcinoma cells by in situ nucleic acid hybridization. An etiological relationship was found between EBV and Burkitt's lymphoma, but not between EBV and Hodgkin's disease or Kaposi's sarcoma. (no refs)

78-5242 **Relation of Herpesvirus Hominis Type II to Carcinoma of the Cervix: An Animal Model for the Induction of Long-Term Latency of Herpesvirus Hominis Type II.** (Eng) Tobin, S. M. (Dept. Res., Mount Sinai Hosp., 600 University Ave., Toronto, Ontario M5G 1X5, Canada); Wilson, W. D.; Fish, E. N.; Papsin, F. R. *Obstet Gynecol* 51(6): 707-712; 1978.

An animal model was developed to demonstrate the long-term persistance of acute herpesvirus hominis type II (HVH-II) vaginocervical infection, one of the conditions that must be proved if HVH-II is to be considered an etiologic factor in carcinoma of the cervix. Female Wistar rats and female Balb/c mice were infected with HVH-II. Acute herpetic infection of the cervix was verified by several techniques: cytopathic effects (CPE), serum antibody titers to HVH-II, cytologic examination of cervical squamous epithelial cells, and indirect double-antibody immunofluorescence staining. Rats and mice that gave a positive result in these tests were maintained for 30 and 18 mo, respectively, after which they were sacrificed and the pelvic sensory ganglia examined for persistence of HVH-II. Of the ganglia from infected rats and mice, 91.5% and 80.0%, respectively, showed persistance of the virus as determined by CPE and 51.5% and 40.0%, respectively, showed persistance of the virus as determined by immunofluorescent staining. These results indicate that following a proved acute cervicovaginal infection with HVH-II, the virus persists in the local pelvic sensory ganglia of a significant number of animals for the equivalent of 60 human yr. (25 refs)

78-5243 **An Investigation into the Relationship of the Immunological Status of Herpes Simplex Virus Type-2 (HSV-2) Infected Animals and the Tumor-enhancing Property of this Infection.** (Eng) Reiss-Gutfreund, R. J. (Inst. Cancer Res., Univ. Vienna, Vienna, Austria); Dostal, V.; Fanta, D. *Oesterr Z Onkol* 4(2/3): 35-39; 1978.

The immunological status of herpes simplex virus 2 (HSV-2)-infected animals was compared with that of controls by three in vivo tests of cell-mediated immunity plus an in vitro test involving stimulation of DBF_1 mouse splenocytes with phytohemagglutinin (PHA). In the skin-grafting test, C3H mice received tail skin grafts from C57Bl mice and, 48

hr later, were infected with 2.5 x 10^3 plaque-forming units (PFU) of HSV-2 sc. In a footpad test, Swiss mice were infected similarly and inoculated with 50 μg PHA 12 days later. In the tuberculin test, Hartley strain II guinea pigs were inoculated with 10^5 PFU HSV-2 into both hind footpads and sensitized simultaneously with BCG. Thirteen days later, the guinea pigs were inoculated with tuberculin. The skin-grafting and PHA-footpad tests did not reveal any differences in cell-mediated immunity between the test groups and similarly treated, but uninfected, control groups. However, in the tuberculin test, the test animals had a slightly impaired reactivity compared with controls. In addition, in the in vitro PHA assay there was a transient (approx 1 day) reduction of the stimulation index in cultures of splenocytes from virus-infected mice approx 10 days postinfection. This reduction was the result of a low rate of ^{3}H-thymidine incorporation by the PHA-stimulated cultures and a relatively high rate of uptake of ^{3}H-thymidine by the control (unstimulated) cultures. The short-lived immunodeficiency of HSV-2-infected mice might be associated with the tumor-enhancing property of HSV-2, as the time of impairment of cell-mediated immunity was directly correlated with the time of tumor initiation found in previous animal experiments. (26 refs.)

78-5244 **Molecular Genetics of Herpes Simplex Virus: Demonstration of Regions of Obligatory and Nonobligatory Identity Within Diploid Regions of the Genome by Sequence Replacement and Insertion.** (Eng) Knipe, D. M. (Marjorie B. Kovler Viral Oncology Labs., Univ. Chicago, 910 East 58th St., Chicago, IL, 60637); Ruyechan, W. T.; Roizman, B.; Halliburton, I. W. *Proc Natl Acad Sci USA* 75(8): 3896-3900; 1978.

The structure of the reiterated regions of the S component of the DNA's of herpes simplex viruses 1 and 2 (HSV-1, HSV-2) were probed in marker rescue experiments involving transfection of cells with mixtures of intact HSV-1 mutant DNA and individual DNA fragments generated by restriction endonuclease digestion of wild-type HSV-1 or HSV-2 DNA. DNA fragments from both reiterated regions of the S component of HSV-1 DNA rescued temperature-sensitive (ts) mutants tsLB2 and tsD. However, only one end of the S component of wild-type HSV-1 rescued tsD, although both ends rescued tsLB2. Recombinants produced with the heterotypic ends of the S complement specified corresponding polypeptides typical of HSV-1 and HSV-2. Several recombinant clones produced by rescue with HSV-2 DNA contained identical HSV-2 DNA insertions within both reiterated regions of the HSV-1 S component. Thus, the reiterated S sequences may contain a region of obligatory identity. HSV DNA could be expended by at least 5 x 10^6 by means of insertion in the S component, suggesting that it could be a vehicle for exogenous DNA. (14 refs.)

78-5245 **Cytoskeletal Proteins in Normal, Infected and Virus-transformed Cells (Meeting Abstract).** (Eng) Gabbiani, G. (Dept. Pathology and Molecular Biology Univ. Geneva, CH-1211 Geneva, Switzerland); Borgia, R Chaponnier, C.; Rungger, E.; Weil, R. *Experientia* 34(7): 940 1978. (no refs)

78-5246 **Forms of Intracellular SV40 DNA-Protei Complexes (Meeting Abstract).** (Eng) Fanning E. (Fachbereich Biologie, Universitat Konstanz, Postfach 7 33, D-7750 Konstanz, W. Germany); Baumgartner, I Klempnauer, K. H.; Richter, A.; Otto, B. *Hoppe Seylers Physiol Chem* 359(9): 1081; 1978. (4 refs)

78-5247 **Selective Extraction of Replicating Simia Virus 40 Nucleoprotein Complexes from BSC Monkey Cells (Meeting Abstract).** (Eng) Adams, R. I (Dept. Biochemistry, Univ. Glasgow, Glasgow G12 8QQ Scotland); Eason, R.; Digges, I.; Lindsay, J. G.; Wolstencrof L. *Hoppe Seylers Z Physiol Chem* 359(9): 1051-1171; 1978 (4 refs)

78-5248 **Phenotypic Complementation of the SV40 *ts* Mutant Defect in Viral DNA Synthesis Follow ing Microinjection of SV40 T Antigen.** (Eng) Kriegler, M P. (Div. Medical Oncology, Sidney Farber Cancer Inst., Bos ton, MA, 02115); Griffin, J. D.; Livingston, D. M. *Cell* 14(4) 983-994; 1978.

To determine whether the simian virus 40 (SV40) A gen product, the large tumor (T) antigen, is involved in the initia tion of viral DNA replication, African green monkey CV-1 cells were microinjected with highly purified SV40 T antige using protein-labeled RBC ghosts and polyethylene glycol a fusagen. The microinjected cells were then infected with temperature-sensitive SV40 mutant (*tsA209*) that is defectiv in the initiation of viral DNA synthesis. In situ hybridizatio assays indicated that microinjection of both partially an highly purified T antigen increased the amount of viral DNA sequences in the monolayer. Furthermore, ^{3}H-thymi dine-labeled and unlabeled Hirt supernatant from microin jected, *tsA209*-infected cells contained significantly mor SV40 DNA than comparable extracts from sham-injected *tsA209*-infected or uninfected cells. Thus, the introduction o highly purified large SV40 T antigen led to phenotypic com plementation of the *tsA* defect in viral DNA synthesis. (3 refs.)

78-5249 **Complete Nucleotide Sequence of SV40 DNA** (Eng) Fiers, W. (Lab. Molecular Biology, Univ Ghent, Ghent, Belgium); Contreras, R.; Haegeman, G. Rogiers, R.; Van de Voorde, A.; Van Heuverswyn, H.; Van Herreweghe, J.; Volckaert, G.; Ysebaert, M. *Natur* 273(5658): 113-120; 1978.

e entire nucleotide sequence of simian virus 40 (SV40) IA (strain 776), a supercoiled circular duplex of 5,224 base rs, was determined. It is estimated that at least 15.2% of genome is not translated into polypeptides. DNA replica- initiates bidirectionally from approx position 0.67 and ninates on the other side of the circle, where the two re- ation forks meet. The half-circle from 0.67 to 0.17, re- ated and transcribed counterclockwise, corresponds al- st exactly to the early region, but the segment from 0.67 0.17, replicated and transcribed clockwise, corresponds to late region. The early t and T antigens are initiated at the ne position, and the T antigen is coded by two noncontigu- regions of the genome; the T antigen messenger RNA RNA) is spliced in the coding region. In the late region, gene for the major protein VP_1 overlaps those for VP_2 and by over 122 nucleotides, but it is read in a different frame. s thought that the mRNA's for these three proteins are ced out of a common primary RNA transcript. The use degenerate codons is nonrandom, but it is similar in both early and late regions. Codons such as NUC, NCG, and N are absent or very rare. (99 refs)

5250 **Recently Replicated Simian Virus 40 DNA Is a Preferential Template for Transcription and plication.** (Eng) Green, M. H. (Dept. Biology, Univ. Cali- nia at San Diego, La Jolla, CA, 92093); Brooks, T. L. *J ol* 26(2): 325-334; 1978.

e template activities for replication and transcription were npared for recently replicated (new) and uniformly labeled l) simian virus 40 (SV40) DNA in TC7 infected monkey s. New SV40 DNA (pulse-labeled for 1 hr) served as a plate for a second round of replication with a relatively h probability (8% of the DNA replicated per hour) for eriod of 5 hr; after this time, the template activity rapidly reased severalfold. Old SV40 DNA (labeled for 24 hr) ctioned as a template for replication with a constant prob- lity (1.8% of the DNA replicated per hour) for at least hr. The proportion of RNA polymerase associated with nreplicated and with recently replicated (bromodeoxyuri- e-substituted) viral DNA was determined by an assay that d the Triton-soluble SV40 transcription complex. The portion of RNA polymerase associated with nonreplicat- SV40 DNA decreased very slowly (to 50% in 6 hr); this gested that replicating viral genomes are not required as plates for the initiation of late transcription. This sugges- n was supported by the finding that the RNA synthesized vitro was associated with covalently closed circular SV40 NA. Furthermore, after 9 hr in bromodeoxyuridine, the ently replicated viral DNA had nearly three times more NA polymerase per unit of DNA than did the nonreplicat- DNA. It is concluded that recently replicated SV40 DNA preferentially utilized as a template for transcription and lication. (36 refs)

-5251 **An Immunochemical Investigation of SV40 T Antigens. 1. Production Properties and Specificity of a Rabbit Antibody to Purified Simian Virus 40 Large-T Antigen.** (Eng) Lane, D. P. (Dept. Zoology, Imperial Coll., London SW7 2AZ, England); Robbins, A. K. *Virology* 87(1): 182-193; 1978.

The specificity of a rabbit antiserum to purified large tumor (T) antigen, a polypeptide of simian virus 40 (SV40), was compared with that of hamster antitumor serum to gain insight into the specificity of the hamster immune response to an SV40-transformed cell-induced tumor (H65). (T antigen has an apparent mol wt of 84,000 or 94,000 daltons, depending on the extraction method.) Immune complexes of SV40-infected monkey kidney cell extracts and hamster antitumor sera were isolated and analyzed on sodium dodecyl sulfate-polyacrylamide gels. A band of 84,000 apparent mol wt that was strongly stained by Coomassie blue was obtained. The rabbit antiserum bound specifically to a 94,000-mol wt polypeptide present in the transformed H65 cell line. The hamster antitumor serum also bound to these components in extracts of transformed or lytically infected cells. Both rabbit anti-T serum and hamster anti-tumor serum specifically bound up to 80% of a purified 94,000-mol wt T antigen that had been isolated by prior immunoprecipitation with a hamster antitumor serum. Native T antigen was heat-stable and resistant to denaturation. The rabbit anti-T serum specifically precipitated an additional low-mol wt (19,000 daltons) polypeptide (small T antigen). This same component was precipitated by the hamster antitumor serum, and it was found during the course of an SV40 lytic infection and in SV40-transformed cells. The data indicated that t and T antigens share common antigenic determinants. A third species of 60,000 mol wt was also specifically precipitated by both the rabbit anti-T serum and hamster antitumor serum; its relationship to t and T is not known. (37 refs)

78-5252 **New Region of the Simian Virus 40 Genome Required for Efficient Viral Transformation.** (Eng) Bouck, N. (Dept. Microbiology, Univ. Illinois at Medical Center, Chicago, IL, 60680); Beales, N.; Shenk, T.; Berg, P.; di Mayorca, G. *Proc Natl Acad Sci USA* 75(5): 2473-2477; 1978.

The transformation of normal nonpermissive rat cells (F111) to anchorage independence was measured after they were infected with viable mutants of simian virus 40 (SV40) that had deletions in three regions of the virus genome: map coordinates 0.21-0.17, 0.59-0.54, and 0.67-0.74. Only those mutants whose deletions occurred between 0.59 and 0.55 in the proximal part of the early region were defective in transforming ability. The most severely defective mutants transformed with less than one-hundredth the efficiency of wild-type virus. These mutants retained their defect when tested in Chinese hamster lung cells and when infection was initiated with viral DNA instead of intact virions. Complementation for transformation was observed between these transformation-defective deletions and an SV40 temperature-sensitive A mutant. (31 refs)

78-5253 **Replication of Simian Virus 40 in Simian Virus 40-transformed Hamster Kidney Cells Induced by Mitomycin C or ^{60}Co γ Irradiation.** (Eng) Rakusanova, T. (Dept. Medicine, Massachusetts General Hosp., Boston, MA, 02114); Smales, W. P.; Kaplan, J. C.; Black, P. H. *Virology* 88(2): 300-313; 1978.

The kinetics of simian virus 40 (SV40) DNA replication and late virus protein synthesis were examined in various clones of induced SV40-transformed Syrian golden hamster kidney (SV-HK) cells and compared with those in lytically infected, permissive, monkey (SV-PM) cells. Virus yields in the SV-HK cells obtained after induction with ^{60}Co γ-radiation (250 rads/sec) or mitomycin C (0.5 μg/ml) were low, and the clones were heterogeneous for infectious virus induction. To investigate the reason(s) for the heterogeneity and low virus yields, the extent of SV40 replication and production of virion (V) antigen and infectious virus after induction were examined. Cells replicating SV40 DNA or synthesizing V antigen were determined by in situ hybridization and immunofluorescence, respectively. Only some cells in induced cultures produced SV40, and those that did were less efficient than SV-PM cells. The inducers acted by inducing more cells to replicate virus rather than by increasing the amount of SV40 released from individual cells. In all clones studied, a greater proportion of cells could be induced to replicate SV40 DNA than to synthesize V antigen. Furthermore, SV40 DNA replication could be induced by lower doses of γ-radiation than could the production of V antigen or infectious virus, which suggests that, in induced cells, synthesis of late virus protein is more restricted than SV40 DNA replication. Thus, one of the effects of induction of SV-HK cells was an enhancement of the cells' capacity to support SV40 replication. (19 refs.)

78-5254 **Biochemical and Ultrastructural Analysis of SV40 Chromatin.** (Eng) Keller, W. (Cold Spring Harbor Lab., Cold Spring Harbor, NY, 11524); Muller, U.; Eicken, I.; Wendel, I.; Zentgraf, H. *Cold Spring Harbor Symp Quant Biol* 42(part 2): 227-244; 1978.

Simian virus 40 (SV40) chromatin containing a full complement of histone H1 in addition to the intranucleosomal histones H2A, H2B, H3, and H4 was isolated from SV40-infected African green monkey kidney CV1 cells and characterized. SV40 chromatin isolated at moderate ionic strength (μ = 0.1-0.3) contained all five histones and appeared highly condensed under the electron microscope: it was composed of a few closely connected large spheres with an av diameter of 190 A (range 160-220 A). At high ionic strength (μ = 0.6-0.8) or after prolonged exposure to very low ionic strengths (μ < 0.02), the compact form unfolded and the chromatin exhibited a typical nucleosomal morphology. Native SV40 DNA-protein complexes contained a median number of 24 nucleosomes. The number of superhelical turns did not differ in DNA obtained from the compact and the unfolded forms of chromatin. DNA-relaxing enzyme was found to be associated with SV40 chromatin, and it w capable of acting both on extraneously added circular DN and on its own DNA in the nucleoprotein complex. Purifi DNA-relaxing enzyme formed transiently nicked DNA i termediates, and the enzyme could be found covalently a tached to the site of the nick in the DNA. Transcriptiona active SV40 complexes underwent the same ion strength-dependent structural transition as that of bulk SV chromatin and, therefore, it may also have a compact co figuration at physiological salt concentrations. (71 refs.)

78-5255 **A Novel Sequence Arrangement of SV40 La RNA.** (Eng) Hsu, M. T. (Rockefeller Uni New York, NY, 10021); Ford, J. *Cold Spring Harbor Sym Quant Biol* 42(part 2): 571-576; 1978.

The 16S and 19S late messenger RNA's (mRNA's) of simi virus 40 (SV40) were mapped on the SV40 genome. The sim ple technique used is as follows: SV40 form-I DNA w cleaved with *Eco*RI endonuclease to generate full-length li ear molecules. Subsequent treatment of these linear DN molecules with exonuclease III exposed SV40 DNA s quences complementary to the 5′ end of the mRNA mol cules. Hybrids between the mRNA and exonuclease-treat DNA could be observed by electron microscope or by g electrophoresis after enzymatic digestion of the hybrid. Th size of the RNA-DNA hybrid defined the distance betwe the *Eco*RI site and the 5′ ends of mRNA. Both the 16s an 19s late mRNA's had a 5′ spliced sequence derived from DNA region not immediately adjacent to the main codi region of the RNA. Within the precision of the techniqu the 5′ leader of both mRNA species is concluded to b derived from the region of the SV40 genome from 0.70 to 0.7 map unit. (13 refs.)

78-5256 **Assembly of SV40 and Polyoma Min chromosomes During Replication.** (Eng) Crem si, C. (Dept. Molecular Biology, Institut Pasteur, 75015 Pa is, France); Chestier, A.; Yaniv, M. *Cold Spring Harbor Sym Quant Biol* 42(part 2): 409-416; 1978.

The assembly of simian virus 40 (SV40) and polyoma viru minichromosomes during replication was studied using Afr can green monkey kidney CV1 cells and 3T6 mouse fibro lasts infected with SV40 and polyoma virus. The replicatin intermediates of the viral DNA were associated with histon in the form of nucleosomes in both the parental and daught double-helical DNA. Newly synthesized histones were pre erentially associated with these replicating intermediates an did not exchange with the majority of the histones preser on the mature complexes. Polyoma viral DNA that replica ed in the absence of protein synthesis contained an av of 1 nucleosomes; this suggested that parental histones are redi tributed between the two newly replicated viral DNA mol cules. Their repartition on the newly replicated viral DN appeared to be partially cooperative. (37 refs.)

78-5257 **Nucleosome Structure II: Structure of the SV40 Minichromosome and Electron Microscopic Evidence for Reversible Transitions of the Nucleosome Structure.** (Eng) Oudet, P. (Laboratoire de Genetique Moleculaire des Eucaryotes du CNRS, U.44 de l'INSERM, Institut de Chimie Biologique, Faculte de Medecine, 67085 Strasbourg Cedex, France); Spadafora, C.; Chambon, P. *Cold Spring Harbor Symp Quant Biol* 42(part 2): 301-312; 1978.

Simian virus 40 (SV40) minichromosomes extracted from CV1 cells were used as a model for chromatin in studies to determine whether the compact nucleosomal form of chromatin could be opened and extended in a reversible manner that would not involve the complete disruption of the histone-DNA bonds. Electron microscopic evidence indicates that at very low ionic strength, nucleosomes can open into half-nucleosomes and more extended, morphologically disorganized, structures. However, these structural transitions were readily reversible, and the basic repeat structure of the chromatin was preserved upon micrococcal nuclease digestion, even when the highly ordered nucleosomal appearance had disappeared. Recent findings relating to the nucleosomal structure of the SV40 minichromosome are summarized. (35 refs.)

78-5258 **Stimulation of Ribosomal RNA Synthesis in Isolated Nuclei and Nucleoli by Partially Purified Preparations of SV40 T Antigen.** (Eng) Baserga, R. (Fels Res. Inst., Temple Univ. Sch. Medicine, Philadelphia, PA, 19140); Ide, T.; Whelly, S. *Cold Spring Harbor Symp Quant Biol* 42(part 2): 685-691; 1978.

The ability of partially purified simian virus 40 (SV40) tumor (T)-antigen preparations to stimulate RNA synthesis in the isolated nuclei and nucleoli of resting rat liver cells was determined. Addition of T-antigen preparations isolated from SV40-transformed cells to the nuclei and nucleoli resulted in the stimulation of ribosomal RNA (rRNA) synthesis; most of the stimulation was due to an increased synthesis of rRNA precursors. Isolated nuclei had to be preincubated with T-antigen preparations for at least 20 min to obtain a good stimulation, but a 5-min preincubation was sufficient to produce a max stimulatory effect in nucleoli. These findings combined with those in the literature make SV40 T antigen the virally directed counterpart of the hypothetical protein that is induced by serum stimulation and that activates rRNA synthesis in density-inhibited normal cells stimulated to proliferate. These findings could also explain, at least partly, the mechanism of viral transformation. T antigen is expressed in SV40-transformed cells, and it is hypothesized that its presence continually stimulates the nucleolus of the transformed cells. This continuous interaction would keep the transformed cells from entering G_0. The cells would then continue to grow until the nutritional conditions became such that they could not sustain growth and cell death would result. (66 refs.)

78-5259 **Density-Dependent Regulation of Amino Acid Transport in SV40-Transformed 3T3 Cells (Meeting Abstract).** (Eng) Borghetti, A. F. (Istituto di Patologia Generale, Universita di Parma, Via Gramsci 14, I-43100 Parma, Italy); Piedimonte, G.; Tramacere, M.; Guidotti, G. G. *Hoppe Seylers Z Physiol Chem* 359(9): 1061-1062; 1978. (11 refs)

78-5260 **Synthesis and Degradation of Simian Virus 40 RNA Sequences Not Found in the mRNA Population.** (Eng) Fried, A. H. (Institut fur Virusforschung, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, 6900 Heidelberg 1, W. Germany). *Virology* 88(2): 286-299; 1978.

The synthesis and degradation of a class of RNA sequences, referred to as dRNA sequences, which are transcribed from the late DNA strand of simian virus 40 (SV40) along with late messenger RNA (mRNA), were analyzed. The RNA isolated from SV40-infected CV-1 monkey cells was pulse-chase labeled with ^{3}H-uridine, the total cellular RNA extracted, and the RNA hybridized against the late strands of restriction endonuclease fragments of SV40 DNA that specifically hybridize to dRNA or mRNA sequences. Minimum estimates of the relative rate of synthesis of the dRNA sequences, compared to that of the mRNA sequences, were obtained from the relative amounts of radioactivity in these sequences following 10 min of labeling. These minimum estimates ranged from 0.32 to 0.55 and depended both on the individual labeling experiment and on which DNA fragments were used to assay for the dRNA and mRNA sequences. With longer chase periods, the ratio of labeled dRNA to that of labeled mRNA decreased, suggesting that the former are less stable than the latter. Further studies indicated that the dRNA was being degraded. In contrast to a previous report, sedimentation analysis of pulse-labeled RNA in dimethyl sulfoxide did not reveal more than minor amounts of labeled multilength transcripts of the late DNA strand. (35 refs)

78-5261 **Experimental (JC Virus-Induced) Intraocular and Extraocular Orbital Tumors in the Syrian Hamster (Meeting Abstract).** (Eng) Ohashi, T. (Univ. Wisconsin, Madison, WI); ZuRhein, G. M.; Varakis, J. N.; Padgett, B. L.; Walker, D. L. *J Neuropathol Exp Neurol* 37(5): 667; 1978. (1 ref)

78-5262 **Minichromosome from BK Virus as a Template for Transcription In Vitro.** (Eng) Meneguzzi, G. (Faculte des Sciences, Centre de Biochimie, Nice, France); Pignatti, P. F.; Barbanti-Brodano, G.; Milanesi, G. *Proc Natl Acad Sci USA* 75(3): 1126-1130; 1978.

BK virus (BKV) DNA was isolated from infected Vero cells

as a nucleoprotein complex containing about 20 nucleosomes and studied. This "minichromosome" had an av sedimentation coefficient of 55S-60S; no naked DNA was seen in any of the gradient fractions. No endogenous RNA synthesis activity was detected in the absence of added RNA polymerase. Addition of this polymerase indicated that both initiation and elongation of RNA chains are reduced by the presence of nucleosomes. Digestion of BKV DNA by the restriction endonuclease *Hin*dIII into four segments and hybridization analysis of the RNA indicated that with superhelical DNA as the template, all regions of the BKV genome were equally transcribed. With the minichromosome as the transcription template, however, transcription occurred preferentially on the largest fragment. No increase in strand selection was observed with respect to the transcription of purified superhelical BKV DNA. (39 refs)

78-5263 **Ependymomas, Malignant Tumors of Pancreatic Islets, and Osteosarcomas Induced in Hamsters by BK Virus, a Human Papovavirus.** (Eng) Corallini, A. (Inst. Microbiology, Univ. Ferrara, Via Luigi Borsari 46, I-44100 Ferrara, Italy); Altavilla, G.; Cecchetti, M. G.; Fabris, G.; Grossi, M. P.; Balboni, P. G.; Lanza, G.; Barbanti-Brodano, G. *J Natl Cancer Inst* 61(3): 875-883; 1978.

BK virus (BKV), a human papovavirus, was injected iv into 73 3-wk-old Syrian golden hamsters. Between 2.5 and 9 mo after inoculation, 60 of the animals developed tumors. The induced neoplasms were ependymoma (47 animals), carcinoma of the pancreatic islets (8), osteosarcoma (6), adenocarcinoma (1), angiosarcoma (1), angioma (1), lymphoma (1), and seminoma (1). Some of the animals had multip tumors. Hypersecretion of insulin, glucagon, C peptide, and calcitonin was detected in the pancreatic islet tumors. A BKV etiology of the tumors was supported by the following evidence: (1) No tumors with BKV-specific markers appeared in animals given injections of buffer, in animals inoculated with BKV neutralized by anti-BKV-specific serum, or in uninoculated controls; (2) BKV tumor (T) antigen was detected by immunofluorescence and complement fixation tests in tumors of animals inoculated with infectious BKV and in transplanted tumors; (3) antibodies to BKV T antigen were detected in sera of animals bearing primary or transplanted tumors; (4) BKV could be activated by Sendai virus-mediated fusion of neoplastic cells with susceptible Vero cells; and (5) no endogenous hamster oncornaviruses were found in the tumors. (38 refs.)

78-5264 **Polyoma and Other Virus Infections Following Bone Marrow Transplantation for Aplastic Anaemia.** (Eng) Henry, K. (Bone Marrow Transplant Team, Westminister Hosps., London, England). *Pathol Biol (Paris)* 26(1): 55-56; 1978.

The case of a 16-yr-old girl with severe aplastic anemia whose course was complicated by graft-vs-host reaction (GVHR) and fluctuating mental symptoms after a bone marrow trans plant from a compatible sister is presented. Polyoma virion and oncornaviruslike particles were discovered via negativ stain of the urine sediment. The polyoma virus was of the BK strain. Comprehensive virological screening is suggested fo both donor and recipient. (3 refs)

78-5265 **A Mouse Embryo Cell Line Carrying an Indu cible, Temperature-sensitive, Polyoma Viru Genome.** (Eng) Bourgaux, P. (Departement de Microbiolo gie, Faculte de Medicine, Centre Hospitalier Univeristair Universite de Sherbrooke, Sherbrooke, Quebec, Canada J1 5N4); Delbecchi, L.; Yu, K. K.; Herring, E. *Virology* 88(2 348-360; 1978.

Transformed (Cyp) cells were obtained by exposing secon ary cultures from whole albino Swiss mouse embryos to temperature-sensitive (ts) mutant of polyoma (Py) virus (P155, 1 plaque-forming unit/cell) at the restrictive temper ture (38 C). At this temperature, *ts*-P155 transforms but r plicates poorly. The cultures were then passaged at 39 C the presence of Py virus antiserum until sufficient cell dege eration occurred (approx 4 mo later) to allow detection of foci of cells exhibiting lack of contact inhibition. One su focus gave rise to the Cyp strain, which was cloned after passages in vitro. No significant differences in phenoty were observed among any of the clones or between clon and uncloned cells. At 39 C, they displayed several properti of transformed cells and, as indicated by indirect immun fluorescence, were negative for virus antigen and clearly po tive for tumor (T) antigen. They did not produce detectal amounts of viral DNA and they produced only low amou of viral hemagglutinin, although they were still fully perm sive for Py virus replication. Exposure of Cyp cells to nonrestrictive temperature (33 C) resulted in an extens cytopathic effect within 30-34 hr that was concurrent w the production of large amounts of infectious, *ts*, Py vir T-antigen synthesis was even more pronounced. Covalen closed viral DNA molecules sedimenting at 53S were synt sized; max levels were reached 32-34 hr after transfer to 33 Cleavage by *Hpa*II yielded fragments characteristic of parent virus strain of *ts*-P155. Py virus antiserum neither c tailed the cytopathic effect nor depressed viral DNA synt sis, although it suppressed virus production. The highly e cient induction of virus replication by the Cyp cells at 3 and the temperature sensitivity of the rescued virus sugg that Cyp cells are not carrying a revertant of the *ts*-P genome. (49 refs)

78-5266 **Neoplastic Transformation of Hamster G Cells by Polyoma Virus (Meeting Abstra** (Eng) Hassoun, J. (Laboratoire de Neuropathologie, Facu de Medecine, Marseille, France); de Micco, C.; Tripier, F.; Toga, M. *J Neuropathol Exp Neurol* 37(5): 624; 1978. refs)

-5267 **The Frequencies of Transcription from the E- and L-Strands of Polyoma DNA.** (Eng) ır-Shavit, R. (Dept. Genetics, Weizmann Inst. Science, ehovot, Israel); Laub, O.; Aloni, Y. *J Gen Virol* 39(2): 7-360; 1978.

xhaustion-type hybridization was used to measure the nount of nuclear virus RNA complementary to the early E) and late (L) polyoma virus DNA strands. 3T-6 cells were fected with 2 ml of stock virus (10^8 plaque-forming nits/ml), and the infected cells were labeled at 30 hr postinction with ^{3}H-uridine. At 36 hr postinfection, 2.5%-7.3% the newly synthesized virus RNA was complementary to e E-strand (-strand) and 92.7%-97.5% was complementary the (L-strand) (+strand). This proportion was independnt of labeling time, indicating similar accumulation of the -RNA and L-RNA transcripts in the nucleus. These findgs indicate that the transcription of polyoma virus DNA regulated in a manner similar to that of simian virus 40 NA. Thus, at least two control mechanisms are at work. ne is at the transcriptional level and it determines the freıencies of transcription from each strand, and the second at the posttranscriptional level and it determines the stabili- of the primary transcripts and the choice of specific fragents transported to the cytoplasm. (13 refs)

8-5268 **Cellular Alterations Dependent upon the Polyoma Virus Hr-t Function: Separation of Mitogenc from Transforming Capacities.** (Eng) Schlegel, R. (Dept. athology, Harvard Medical Sch., Boston, MA, 02115); Benamin, T. L. *Cell* 14(3): 587-599; 1978.

he role of the hr-t polyoma virus gene in inducing properties f transformation was explored by studying the early phase f nonproductive infection in cells infected by wild-type virus, r-t mutants, and ts-a mutants. Within the first 24 hr after nfection by wild-type or ts-a mutant virus, a transformed henotype consisting of stellate cell shape, loss of organized ytoplasmic actin cables, nuclear and nucleolar enlargement, nd behavioral changes such as cellular underlapping became vident. Cells infected by hr-t mutants underwent none of hese changes and remained morphologically indistinguishale from mock-infected cultures. Wild-type virus and hr-t nutants induced cellular DNA synthesis in confluent nonolayers of rat cells beginning 12-14 hr postinfection. here was a virus-mediated transit of cells from the G1 to he S and G2 phases of the cell cycle and an increase in the roportion of cells with an octaploid DNA content. Infection y wild-type virus gave rise to nearly 50% polyploid clones, nost of which were not stably transformed. Less than 5% f the clones derived from the mock-infected and hr-t muant-infected cultures were polyploid, and no transformants vere found. The hr-t mutants promoted only a single round f cell division, whereas the wild-type virus and ts-a mutants romoted multiple rounds. Thus, loss of the hr-t function in olyoma virus results in a residual viral mitogenic activity but prevents the virus from effecting the morphological transformation of cells. (46 refs.)

78-5269 **Detection of Airborne Polyoma Virus.** (Eng) McGarrity, G. J. (Inst. Medical Res., Camden, NJ); Dion, A. S. *J Hyg (Camb)* 81(1): 9-13; 1978.

The detection of airborne polyoma virus in an animal laboratory housing mice infected with the virus is described. Air samples were obtained by a high-volume air sampler, and the samples were concentrated by high-speed centrifugation. Polyoma virus was assayed by mouse antibody production tests, and it was found in 4/6 samples. (8 refs.)

78-5270 **Absence of C-Type Virus Production in Human Leukemic B Cell, T Cell and Null Cell Lines.** (Eng) Ogura, H. (Dept. Virology, Cancer Inst., Okayama Univ. Medical Sch., Okayama 700, Japan); Hiraki, S.; Omura, S.; Miyoshi, I.; Oda, T. *Acta Med Okayama* 32(2): 169-172; 1978.

Electron microscopy and enzymatic and biological techniques were used to determine whether C-type RNA virus is produced in human leukemic B-cell (BALL-1), T-cell (TALL-1), and null cell (NALL-1) lines. The results of the electron microscope studies and of an assay for reverse transcriptase activity in the culture supernatants were negative. Next, an attempt was made to amplify any possible human leukemia virus in the cells by cocultivation of the three lines with a bat lung cell line (BAT/88), which propagates primate C-type virus well. After 3 wk of cocultivation, the culture supernatants were again examined for reverse transcriptase activity and the cells were tested for syncytia formation in XC, KC, and RSb cells. All of these tests, except for those using a positive control (simian sarcoma virus-simian sarcoma-associated virus), were negative. It is concluded that the three human leukemic cell lines do not produce C-type RNA virus, although it is possible that the virus is present in a masked form in these lines. (16 refs.)

78-5271 **Analysis of RNA Tumor Virus Genomes.** (Eng) Haseltine, W. A. (Sidney Farber Cancer Inst., Boston, MA, 02115); Kleid, D. G.; Pedersen, F. S. *In: Advances in Comparative Leukemia Research 1977. Proceedings of the VIIIth International Symposium on Comparative Research on Leukemia and Related Diseases, held in Amsterdam, The Netherlands on 22-26 August, 1977.* Bentvelzen, P.; Hilgers, J.; Yohn, D. S., eds. (New York: Elsevier/North Holland Biomedical Press): 503 pp.; 437-442; 1977.

RNA tumor viruses were divided into four groups according

to the length of the runoff product (strong-stop DNA) produced by transcription of 70S viral RNA's with avian myeloblastosis virus reverse transcriptase. Group 1 comprised murine, woolly gibbon, and feline viruses; Group 2, endogenous baboon viruses and endogenous feline viruses; Group 3, chicken viruses; and Group 4, murine mammary tumor virus. On the basis of the oligopyrimidine composition of the strong stop DNA, the murine, woolly gibbon, baboon, and feline RD114 viruses were then divided into subgroups that show the extent of sequence divergence within the main groups. Preliminary data are also presented on the T_1-resistant oligonucleotides shared by viruses isolated from preleukemic or leukemic AKR mice. The viruses are AKV-1, AKV-2, AKR-247 CN-tropic xenotropic virus from a preleukemic mouse, and MB-34, a similar isolate from a mouse partially congeneic for the AKV-Z genomes. (9 refs)

78-5272 **Abolition of Lymphocyte Blastogenesis by Oncornaviral Components (Meeting Abstract).** (Eng) Hellman, A. (VOP, NCI, Frederick, MD); Fowler, A, K.; Twardzik, D. R.; Weislow, O. S. *J Reticuloendothel Soc* 23(6): 37i; 1978. (no refs)

78-5273 **Relationship Between A-Type and C-Type Particles in Ehrlich Ascites Tumor Cells.** (Eng) Chew, E. C. (Dept. Anatomy, Univ. Hong Kong, Hong Kong). *Experientia* 34(8): 1086-1088; 1978.

Electron microscopy of Ehrlich ascites tumor cells obtained from the peritoneal fluid and im implants of mice carrying the tumor revealed intracisternal A-type particles in the cytoplasm. On rare occasions, intracytoplasmic A particles were also detected. In addition, mature and immature C-type particles were observed in some tumor cells. Many mature C-type particles were found only in the intercellular space. (14 refs.)

78-5274 **Search for Infective Mammalian Type-C Virus-related Genes in the DNA of Human Sarcomas and Leukemias.** (Eng) Nicolson, M. O. (Div. Infectious Diseases and Virology, Children's Hosp., Los Angeles, CA); Gilden, R. V.; Charman, H.; Rice, N.; Heberling, R.; McAllister, R. M. *Int J Cancer* 21(6): 700-706; 1978.

Transfection techniques were used to study the infectivity of proviral DNA's of C-type murine, gibbon, and baboon viruses in human and dog cells. DNA's from four gibbon tissues (liver, lung, skin-muscle, and kidney) and from baboon embryo fibroblast strains BEF No. 1 and BEF No. 2 did not transfect TE-32 human sarcoma cells or D-17 dog cells. DNA's from two baboon placentas and from BEF No. 3, containing 100 viral genome equivalents per haploid cellular genome, transfected D-17 but not TE-32 cells. TE-32 and D-17 cells experimentally infected with baboon virus contained only five genome equivalents per haploid cellular genome, but they released high titers of infectious virus. The DNA's of these cells contained baboon proviruses infectious for both TE-32 and D-17 cells. Proviruses were not detectable in any of the DNA's of human sarcoma or leukemia cells tested. (46 refs)

78-5275 **DNA Viruses in Urine after Renal Transplantation.** (Eng) Lecatsas, G. (Dept. Microbiology, Inst. Pathology, Univ. Pretoria, P.O. Box 2034, Pretoria 0001, Republic South Africa); Van Wyk, J. A. *S Afr Med J* 53(20): 787-788; 1978.

Over a 5-yr period, approx 2,500 urine specimens from 96 renal transplants were examined for virus particles. Electron microscopy of negatively stained preparations showed that only three virus groups were present: polyoma virus (36 patients), herpesvirus (10), and adenovirus (11). The failure to detect RNA viruses suggests that they are absent or may require different means of activation. (13 refs)

78-5276 **Localization of Hepatitis B Surface Antigen in Neoplastic Cells of Primary Hepatocellular Carcinoma (Meeting Abstract).** (Eng) Murugasu, R. (Royal Newcastle Hosp., Newcastle, England). *Pathology* 10(2): 196-197; 1978. (no refs)

3-5277 **Sequence Variation among Heavy Chains from Inulin-binding Myeloma Proteins.** (Eng) Vrana, . (Lab. Cell Biology, NCI, NIH, Bethesda, MD, 20014); udikoff, S.; Potter, M. *Proc Natl Acad Sci USA* 75(4): 57-1961; 1978.

ne entire sequences of the variable region of three heavy ains from BALB/c mouse inulin-binding myeloma pro- ins were determined by cyanogen bromide cleavage and Se- adex G-100 column chromatography. (The variable region quence of the fourth inulin-binding protein has been de- ribed previously). Among the four proteins there are six nino acid differences, all of which occur in the framework rtion of the variable region. All of the six amino acid substi- tions can be explained by single base mutations at the DNA el. Unlike the previously described group of heavy chains m phosphorylcholine-binding myeloma proteins, which ith the exception of 2 that are identical) have size and quence differences in their complementarity regions, the ulin-binding heavy chains all have identical complemen- rity regions, with H3 being extremely short. The pattern variation observed in the antiinulin heavy chains appears be most easily explained by a somatic mutation mech- ism. However, because none of the substitutions occur in mplementarity-determining regions, they presumably ould have no selective advantage and would not alter bind- g specificity. Five of the six sequence differences occur at sitions that are internal in the molecule and thus do not count for previously observed idiotypic differences. The sults suggest that most of the idiotypic cross-reactivities are ue to differences in the light chains of the antiinulin pro- ins. (35 refs)

8-5278 **Shedding of Anti-IgM from Antibody-coated Human Lymphoma Lines: Differences Between pstein-Barr Virus-negative Lines and Their Virus-convert- l Sublines.** (Eng) Yefenof, E. (Dept. Tumor Biology, Karo- nska Institutet, S-104 01 Stockholm 60, Sweden); Lundin, .; Klein, G. *Eur J Immunol* 8(3): 190-193; 1978.

urface IgM-positive, Epstein-Barr virus (EBV)-negative cell nes and their virus-converted sublines were compared with spect to their ability to shed membrane-bound anti-IgM ntibodies, in order to investigate the membrane changes that company EBV conversion. The in vitro converted EBV enome-carrying sublines showed a reduced ability to shed urface-bound antibodies, compared with their EBV-free par- ntal B lymphoma lines. On the other hand, antibody degra- ation was higher in the EBV-positive cells. Analysis of anti- ody-coated single cells indicated that the cells that failed to redistribute or cap their ligand-bound surface components at 37 C were also capable of shedding bound antibody. This finding suggests that capping and shedding are essentially independent phenomena. However, both may be influenced by the same virally induced change in the lateral mobility of membrane constituents. (33 refs)

78-5279 **Further Characterization of the Suppressor Cells, Activated by Goat Anti-Th-B Antibody Reagent and Responsible for Enhanced Growth of Sarcoma 180 in AKR Mice.** (Eng) Kakimoto, K. (Dept. Immunology Res., Roswell Park Memorial Inst., Buffalo, NY, 14263); Fuji, H.; Grossberg, A. L.; Pressman, D. *Cell Immunol* 37(1): 61-76; 1978.

The suppressor cells that enhance the growth of allogeneic sarcoma 180 (S180) in AKR mice previously inoculated with goat anti-Th-B antibody reagent (prepared from antiserum raised in goats against BALB/c myeloma MOPC 104E cells and purified) were characterized. These suppressor cells were T cells, since they carried the Thy-1 antigen on their surface. Treatment of the cells in vitro with anti-Thy-1 plus complement eliminated their ability to enhance tumor growth. The T cells responsible for tumor enhancement did not carry the Th-B determinant. Treating T cells in vitro with goat anti-Th-B antibody reagent plus complement did not abrogate their tumor-enhancing activity. This suggests that the suppressor T cells involved in tumor enhancement are generated by the interaction of anti-Th-B antibodies with precursor suppressor cells that do carry Th-B. Once generated, the active suppressor cells lose the Th-B antigen; this contention is supported by the finding that the thymic precursors of concanavalin A (Con A)-inducible suppressor cells bear Th-B, since they are killed by anti-Th-B plus complement, but active suppressor cells induced by Con A do not carry Th-B, since they are not killed by anti-Th-B plus complement. Evidence also indicated that nonthymic suppressor cell precursors could be activated by anti-Th-B, since spleen cells from anti-Th-B-treated thymectomized mice bearing S180 can transfer the tumor-enhancing effect. It is concluded that mature suppressor cells cause tumor enhancement by suppressing the immune mechanisms responsible for allogeneic tumor graft rejection. (25 refs)

78-5280 **Preleukemic AKR Mice are Selectively IgA-deficient (Meeting Abstract).** (Eng) Mink, J. G. (Dept. Cell Biology and Genetics, Erasmus Univ., Rotterdam, Netherlands); van Muiswinkel, W. B.; de Laat, A.

M.; Benner, R. *Z Immunitaetsforsch* 54(4): 339; 1978. (3 refs)

78-5281 **Demonstration of Humoral Antibodies Against Autologous Glioma Cells in Experimental Rabbit Gliomas (Meeting Abstract).** (Eng) Stavrou, D. (Inst. Veterinary Pathology, Univ. Munich, Munich, W. Germany); Elling, H.; Haglid, K. G. *J Neuropathol Exp Neurol* 37(5): 694; 1978. (no refs)

78-5282 **Specific Suppression of Antigen-reactive Cells in Neonatal Transplantation Tolerance.** (Eng) Holan, V. (Inst. Molecular Genetics, Czechoslovak Acad. Sciences, Flemingovo nam. 2, 166 10 Prague 5, Czechoslovakia); Chutna, J.; Hasek, M. *Nature* 274(5674): 895-897; 1978.

Immunological reactivity was analyzed in two experimental systems of neonatal tolerance in mice involving a disparity in either the entire *H-2* complex or the *D* region only. Tolerance to different strains was induced by inoculation of B10.A newborn mice with spleen cells from B10 or B10.A(2R) mice within 20 hr of birth. The B10.A mice receiving the neonatal injections were grafted with allogeneic skin at 8-9 wk of age, and those that did not reject the graft were used in the study. In each case, cells from the tolerant mice could not be sensitized in vitro to the tolerated antigens. These cells, which were nonreactive in the in vitro cytotoxicity test, could be separated into nonadherent and nylon-adherent cells according to adherence to nylon wool. The former cells, when sensitized in vitro, were cytotoxic, as were the sensitized cells from normal animals. The latter remained nonreactive even after sensitization and, in addition, specifically inhibited the in vitro sensitization of cells from normal animals. (10 refs.)

78-5283 **B and T Lymphocyte Activation by Murine Leukemia Virus Infection (Meeting Abstract).** (Eng) Bendinelli, M. (Inst. Microbiology, Pisa, Italy); Friedman, H. *J Reticuloendothel Soc* 23(6): 28i; 1978. (no refs)

78-5284 **Alveolar Macrophage-Splenic Lymphocyte Interactions Following Chronic Asbestos Inhalation in the Rat (Meeting Abstract).** (Eng) Kagan, E. (Dept. Pathology, Georgetown Univ. Medical Center, Washington, DC); Miller, K. *J Reticuloendothel Soc* 23(6): 24i; 1978. (no refs)

78-5285 **Ultraviolet Light Induced Murine Suppressor Lymphocytes Dictate Specificity of Anti-ultraviolet Tumor Immune Responses.** (Eng) Spellman, C. (Dept. Pathology, Univ. Utah Medical Center, Salt La City, UT, 84132); Daynes, R. A. *Cell Immunol* 38(1): 25-3 1978.

Suppressor lymphocyte activity was investigated in UV- radiated female C3Hf/HeN mice. When normal mice we hyperimmunized with the regressor UV tumor RD 87 a then challenged with progressor tumors, they exhibit cross-protective immunity. However, the adoptive transfer spleen cells from tumor immune mice into UV-irradiat hosts resulted in tumor-specific immunity. Transfer of 3.5 10^7 nylon-nonadherent spleen cells from UV-treated mi into RD 87-hyperimmune animals did not inhibit the antit mor responses. However, when the same number of n lon-nonadherent UV spleen cells were transferred into no mal mice, the animals were unable to reject RD 87. It w then determined whether mice hyperimmunized with o regressor tumor were capable of rejecting a secondary U regressor tumor following x-radiation-induced block of p mary immune responses. The 450-R dose selected render normal mice tumor-susceptible, but it did not inhibit the a titumor responses of hyperimmunized mice to challenge w either of two regressor tumors. Cross-reactive immunity w unaffected in the immune animals. The suppression of anti mor responses in hyperimmune mice could be effected by t adoptive transfer of suppressor cells from UV-treated mi These results are consistent with the suggestion th UV-induced suppressor cells inhibit antitumor responses rected against the common cross-protective tumor-associa antigens. Although many immune interactions may be volved in the antitumor response, ultimately, effective tum rejection may be mediated by cells subject to suppressor control. In vivo, suppression may dominate and cause pot tial effector cells directed against the common antigens remain as committed preeffector cells. In vitro, suppress may be broken, and cross-reactivity may occur as a resul the survival and expression of effector cells directed agai the common antigenic determinants. (44 refs)

78-5286 **Use of Stimulating Capacity of Mixed Ly phocyte Reaction (MLR-S) as a Possible Ma er for the Cell-Origin of Null-Cell Acute Lymphobla Leukaemia.** (Eng) Han, T. (Roswell Park Memorial In New York State Dept. Health, 666 Elm St., Buffalo, N 14263); Minowada, J. *Immunology* 35(2): 333-339; 1978

The stimulating capacity of the mixed lymphocyte react (MLR-S) of fresh leukemic cells from eight patients with n cell acute lymphoblastic leukemia (ALL) and cultured l kemic null cells from five different cell lines was investiga A one-way MLR conducted with a 1:1 ratio of respond cells to stimulating cells revealed that the cells of five of patients were good stimulators but those of the other th were poor. No stimulating capacity of leukemic cells was served in one of the poor stimulators, even though hig numbers of stimulating cells were employed. Three of

ltured leukemic cell lines consistently exerted a very strong mulation on allogeneic lymphocytes. Another line exhibit- a lesser but significant stimulation of one-way MLR. No gnificant MLR-S of the fifth cell line was observed, even th the use of higher numbers of cells. These findings sug- st that leukemic null cells possessing and not possessing a mulating capacity may represent early B- and T-cell pre- rsors, respectively. (28 refs.)

3-5287 **Functional Heterogeneity and T-Cell Dependent Activation of Macrophages from MSV-induced Tumors (Meeting Abstract).** (Eng) Holden, H. T. (Lab. mmunodiagnosis, NCI, Bethesda, MD, 20014); Varesio, L.; aniyama, T. *J Reticuloendothel Soc* 23(6): 39i; 1978. (no fs)

3-5288 **Enhancement of the Growth of a Chemically-induced Fibrosarcoma by Peritoneal Macrages of Normal and Tumor-bearing Mice (Meeting Abract).** (Eng) Gabizon, A. (Dept. Cell Biology, Weizmann st. Science, Rehovot, Israel); Trainin, N. *J Reticuloendoth- Soc* 23(6): 38i; 1978. (no refs)

3-5289 **Idiotype-specific Transplantation Resistance to MOPC-315: Abrogation by Post-immunization hymectomy.** (Eng) Daley, M. J. (Immunobiology Labs., niv. New Mexico, Sch. Medicine, Albuquerque, NM, 7131); Lynch, R. G.; Gebel, H. M. *J Immunol* 120(5): 520-1624; 1978.

udies were undertaken to determine if the thymus plays a le in idiotype-specific myeloma graft resistance. The idi- ype-specific myeloma transplantation resistance induced in ALB/c mice by immunization with the DNP-binding IgA protein produced by plasmacytoma MOPC-315 was ablat- l by postimmunization thymectomy. Sham thymectomy ad no effect. The ablative effect of thymectomy was ob- rved in mice challenged sc with MOPC-315 cells either 3 r 44 days after thymectomy. These observations imply that short-lived thymic effector contributes to idiotype-specific yeloma graft resistance. (34 refs)

3-5290 **Suppression of Host Immunity by Dietary Hypercholesteremia (Meeting Abstract).** (Eng) oria, R. M. (Dept. Microbiology, Medical Coll. Virginia, irginia Commonwealth Univ., Richmond, VA); Kos, W. L.; aplan, A. M. *J Reticuloendothel Soc* 23(6): 49i; 1978. (no fs)

78-5291 **Immunologic Basis of Tumor Dormancy (Meeting Abstract).** (Eng) Wheelock, E. F. (Dept. Microbiology, Thomas Jefferson Univ., Philadelphia, PA). *J Reticuloendothel Soc* 23(6): 38i; 1978. (no refs)

78-5292 **Role of Immunocompetence, Immunosuppression and Social Stress in Susceptibility of Chickens to Rous Sarcoma (Meeting Abstract).** (Eng) Misra, L. K. (Texas A&M Univ., College Station, TX, 77843). *Diss Abstr Int B* 39(1): 7B-8B; 1978. (no refs)

78-5293 **Nonimmune and Immune Surveillance. II. Effect of Recipient's Age, Tumor Immunogenicity, and Neonatal Thymectomy on Tumor Growth Inhibition.** (Eng) Zinzar, S. N. (Lab. Virology, Cancer Res. Center, Acad. Medical Sciences USSR, Moscow 115478, USSR); Svet-Moldavsky, G. J.; Karmanova, N. V. *J Natl Cancer Inst* 61(3): 737-745; 1978.

Suspensions of homogenates of Lewis lung adenocarcinoma, a mammary gland adenocarcinoma, rectal sarcoma SR-1-75, hepatoma H-2-73, and ovarian carcinoma OC-1-75 were implanted sc into newborn and adult (CBA x C57BL/6J)F_1 and BALB/c mice. The growth of the lung and the mammary tumor was inhibited in newborn mice, but the rectal sarcoma grew at the same rate in newborn and adult recipients. Neonatal thymectomy stimulated the growth of the hepatoma in newborns. The degree of tumor growth inhibition was age-dependent: max inhibition was observed in 1- to 6-day-old recipients, but later it gradually decreased. The hepatoma and the ovarian carcinoma, whose growth was inhibited in newborns, and the rectal sarcoma, whose growth was uninhibited, had equally low immunogenicity. The data suggest that newborns possess factors that inhibit tumor growth but that these factors disappear with the increased age of the recipients. (27 refs.)

78-5294 **Inhibition of Lymphoma Growth in the Spleen and Liver of Lethally Irradiated Mice.** (Eng) Iorio, A. (Inst. Hygiene, Chair Virology, Inst. Pharmacology, Univ. Perugia, 06100 Perugia, Italy); Campanile, F.; Neri, M.; Spreafico, F.; Goldin, A.; Bonmassar, E. *J Immunol* 120(5): 1679-1685; 1978.

The growth of murine lymphomas carrying the *H-2d* (LSTRA, P388), the *H-2K* (6C3HED), and the *H-2a* (LAF-17) haplotypes was studied in the spleen and liver of lethally irradiated (850-1,000 R) compatible or allogeneic mice by the ^{125}I-5-iodo-2′-deoxyuridine uptake method. Ac-

cording to the genetic pattern of the *Hh* (hemopoietic-histocompatibility) system, recipient hosts were either susceptible or resistant to bone marrow grafts carrying the same haplotypes as those of the lymphomas studied. Tumor cell growth was impaired in the spleen of irradiated *Hh*-incompatible resistant hosts (eg, P388 into B10, B10.BR, and CBA), suggesting that lymphoma and bone marrow cells could share common *Hh* antigens. However, inhibition of lymphoma growth occurred also in the spleen of irradiated *Hh*-susceptible mice, either *Hh*-compatible (eg, P388 into B10.D2; 6C3HED into AKR or CBA) or *Hh*-incompatible, but genetically unable to respond against bone marrow cells (eg, LSTRA or P388 into C3H, or 6C3HED into BALB/c or SJL). In almost all cases, growth inhibition was absent or weak in the liver. These results suggest that lymphoma cells can express antigens not detectable on normal bone marrow cells that are capable of eliciting radioresistant inhibition of tumors predominantly in the spleens of mice susceptible to marrow grafts of the same genetic origin as that of the lymphomas tested. (38 refs)

5295 **Characteristics of Preleukemia Cells Induced in Mice.** (Eng) Haran-Ghera, N. (Dept. Chemical nunology, Weizmann Inst. Science, Rehovot, Israel); bio, N.; Leef, F.; Goldstein, G. *Cell Immunol* 37(2): -314; 1978.

dies were conducted to determine whether preleukemia s produced by inoculation of mice with radiation leukemia is (D-RadLV) are prothymocytes and whether virus-in- ed preleukemia marrow cells could immunize against nsplanted leukemia cells induced by the same virus. A high portion of irradiated C57BL/6 mice inoculated with RadLV developed overt T cell leukemias originating in the mus; the incidence in unirradiated hosts was much lower. early as 10 days after injection of D-RadLV, the bone rrow contained preleukemia cells that, although not frank- eukemic, would develop into leukemia cells upon transfer- to a specially pretreated recipient mouse. The leukemia s expressed the T-cell surface component Thy-1 ıy-1+), but the preleukemia cells did not. However, the leukemia cells could be induced in vitro by thymopoietin ıbiquitin to become Thy-1+, suggesting that they are pro- mocytes. Unlike leukemia cells, the injection of preleu- nia cells into normal recipients immunized them against nsplants of leukemias induced by the same D-RadLV. It uggested that D-RadLV induces a critical change in pro- mocytes that in a later (Thy-1+) phase of differentiation nanifested in overt leukemia transformation. (18 refs)

-5296 **Trisomy of 1q in Preleukaemia with Progression to Acute Leukaemia.** (Eng) Najfeld, V. edical Genetics, Veterans Admin. Hosp., 4435 Beacon e. S., Seattle, WA, 98105); Singer, J. V.; James, M. C.; ılkow, P. J. *Scand J Haematol* 21(1): 24-28; 1978.

romosome studies were performed on the marrow cells of 8-yr-old man with refractory megaloblastic anemia prior treatment. The cells had trisomy for the long arm of romosome 1, which was translocated to the long arm of mber 11 [46,XY,-11,+t(1:11)(q11 or q12; q25)]. The same ıormality was found in metaphases from eight individual ınulocytic colonies. When the disease progressed into acute elomonocytic leukemia 5 mo later, trisomy of chromo- ne 8 and an extra chromosome number 19 with partial etion were found in addition to the basic chromosome ab- rmality. Fibroblasts grown from marrow biopsy material owed a normal diploid complement, 46,XY. (11 refs.)

78-5297 **Chronic Lymphocytic Leukaemia: Clonal Origin in a Committed B-Lymphocyte Progenitor.** (Eng) Fialkow, P. J. (Medical Service, Veterans Admin. Hosp., 4435 Beacon Ave. S., Seattle, WA, 98108); Najfeld, V.; Reddy, A. L.; Singer, J.; Steinmann, L. *Lancet* 2(8087): 444-446; 1978.

Determination was made of the glucose-6-phosphate dehydrogenase (G-6-PD) types of isolated blood cell populations and normal skin in two patients (patient 1, 47 yr old, patient 2, 72 yr old) with chronic lymphocytic leukemia (CLL) who were heterozygous at the G-6-PD locus. Approx equal amounts of B and A isoenzyme activities were found in skin specimens. In contrast, only type A G-6-PD was found in the B lymphocytes isolated from patient 1. The homogeneity of this preparation of B lymphocytes was confirmed by failure of the cells to stain with peroxidase or to form erythrocyte (E) rosettes, by the presence of monoclonal immunoglobulin (μ and λ) on the cell surfaces, and by the ability of the cells to form rosettes with mouse RBC. The B-cell preparation from patient 2 showed 5% type B and 95% type A G-6-PD. Peroxidase stains were positive in 3% of the cells, indicating some admixture with granulocytes or monocytes, which may have accounted for the small amount of B isoenzyme. These observations indicate that at the time of diagnosis, all CLL cells were descended from one progenitor; ie, the disease has a clonal origin. Approx equal amounts of B and A isoenzymes were found in granulocytes, RBC, platelets, and T lymphocytes. The findings indicate that CLL involves committed B-lymphocyte progenitors and that the disease differs from chronic myelocytic leukemia and other myeloproliferative syndromes, all of which involve multipotent hemopoietic stem cells. (23 refs.)

78-5298 **Acute Myelogenous Leukemia Subsequent to Therapy for a Different Neoplasm: Clinical Features and Response to Therapy.** (Eng) Preisler, H. D. (Dept. Medicine A, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263); Lyman, G. H. *Am J Hematol* 3: 209-218; 1977.

The case records of 10 patients with acute myelogenous leukemia (AML) who had initially been treated for other malignancies are reviewed. These patients differed from those with "spontaneous" AML in that, at the time of diagnosis, they had lower WBC counts, and significantly less cellular bone marrow, and a lower proportion of leukemic cells in the mar-

row. Eight of these patients initially had advanced primary hematologic malignancies with bone marrow involvement. Most had been exposed to extensive radiation therapy and combination therapy (including alkylating agents) during treatment for their primary malignancy. Extensive chromosome changes were observed in 9/10 patients, compared with only about 40% of previously reported spontaneous AML patients. Only 1/9 patients who received chemotherapy attained remission status, and the mean and median survivals from the initiation of chemotherapy were 2.7 and 1.0 mo, respectively. Nine of the 10 patients died as a result of infection. The refractoriness of this form of AML to chemotherapy was borne out by a review of the literature, which revealed only 2 remissions in 32 treated patients. Cytotoxic chemotherapy should be delayed as long as possible in patients whose AML developed subsequent to therapy for another malignancy. (28 refs)

78-5299 **Non-Hodgkin's Lymphoma Terminating in Acute Myelogenous Leukemia.** (Eng) Cavalli, F. (Div. Oncology, Univ. Hosp., Inselspital, CH-3010 Bern, Switzerland); Sonntag, R. W.; Zimmermann, A.; Deubelbeiss, K.; Ryssel, H. J. *Acta Haematol (Basel)* 60(4): 250-256; 1978.

The case report of a 77-yr-old man who developed acute myelogenous leukemia (AML) 5.25 yr after a diagnosis of diffuse histiocytic lymphoma is presented. The disease was initially treated by radiotherapy; later, upon progression of the disease, moderately intensive chemotherapy was instituted. This therapy was given for almost 5 yr. In Hodgkin's disease, radiotherapy followed by chemotherapy has been shown to carry a high risk for developing a second neoplasia. At present, it is not known why AML is less frequently seen in patients with non-Hodgkin's lymphoma (NHL) than in those with Hodgkin's disease or multiple myeloma. However, since the survival of patients with disseminated NHL is much poorer than of those with Hodgkin's disease, the disease may not have time to develop. It is possible that the radiotherapy and chemotherapy of the NHL contributed to the development of AML in this patient. (31 refs.)

78-5300 **Immunological Family Studies in Hodgkin's Disease. Is the Immunodeficiency Horizontally Transmitted?** (Eng) Bjorkholm, M. (Dept. Medicine, Serafimerlasarettet, S-112 83 Stockholm, Sweden); Holm, G.; Mellstedt, H. *Scand J Haematol* 20(4): 297-305; 1978.

Lymphocyte reactivity was evaluated in 27 consanguineous and nonconsanguineous relatives of 12 patients with Hodgkin's disease (HD). The lymphocyte DNA synthesis induced by concanavalin (Con A) was depressed in six patients. Seven of 15 relatives (3 first-degree relatives and 4 spouses) showed a profound impairment in lymphocyte response to Con A stimulation. None of 12 relatives of patients with a norma Con A response was defective in this respect. In relatives o Con A-hyporesponsive patients, there was a small but statisti cally significant decrease in lymphocyte response to poke weed mitogen and purified protein derivative. No differenc in lymphocyte subpopulations was seen. The findings sug gest that an exogenous factor (probably a virus) depressed th mitogen response in relatives of immunodeficient HD pa tients. A possible link between the immunodeficiency and th pathogenesis of HD is discussed. (35 refs)

78-5301 **Lymphoproliferative Disorders in Four Patient Receiving Chronic Diphenylhydantoin Therapy Etiologic Correlation or Chance Association?** (Eng) Matzn er, Y. (Dept. Hematology, Hadassah Univ. Hosp., Jerusalem Israel); Polliack, A. *Isr J Med Sci* 14(8): 865-869; 1978.

The occurrence of angioimmunoblastic lymphadenopath (AL), Hodgkin's disease, and IgG-λ multiple myeloma i four epileptic patients who had been receiving diphenyl hydantoin (DPH) therapy is described, and current knowl edge of the association between DPH therapy and the devel opment of lymphoproliferative disorders is reviewed. Th four patients were the only examples of lymphoplasmacyti disorders encountered among 300 epileptics treated wit DPH at one institution. Case 1, a 26-yr-old woman, was treat ed for 6 mo with DPH before she developed AL. Cessatio of DPH therapy led to remission. Case 2, a 61-yr-old man had received DPH for several years before developing AL He recovered slowly after cessation of the therapy. Case 3 a 22-yr-old man, developed Hodgkin's disease after treatmen with DPH for 5 yr. Discontinuation of DPH and total noda irradiation led to complete remission 1 yr later. Case 4, 54-yr-old man treated with DPH for centrencephalic epileps for >20 yr, developed IgG-λ multiple myeloma. Serum an urine immunoelectrophoresis showed the presence of an IgG λ paraprotein associated with combined IgA and IgM defi ciency. Although the relation between DPH therapy and th development of immunosuppression and lymphoma i well-documented, the role of the drug in the etiology of thes disorders is still controversial. A chance association betwee ingestion of the drug and the development of lymphoma can not be excluded in these cases. (27 refs.)

78-5302 **Multiple Myeloma Terminating in Lymphocyti Leukemia with B-Lymphocyte Membran Markers.** (Eng) Polliack, A. (Dept. Hematology, Kiryat Hadassah, Hadassah Univ. Hosp., Jerusalem, Israel); Napa stek, E.; Eldor, A.; Zvi, A. B.; Bassat, H. B.; Zlotni A. *Am J Hematol* 3: 153-163; 1977.

The development of an acute, rapidly fatal lymphocytic leu kemia in a 64-yr-old woman with kappa light-chain multip myeloma is reported. The leukemia developed after a relativ

hort period of Alkeran therapy and it was fulminant, with apidly fatal course associated with a bleeding diathesis. st of the leukemic cells lacked the ultrastructural features lasma cells but bore readily detectable B-cell markers and embled lymphocytes at various stages of maturation under light, transmission, and scanning electron microscopes. is case might best be regarded as one of myeloma develop- a variant of plasma cell leukemia in which the leukemic s were lymphocytic in type, suggesting a degree of dedif- entiation of the original malignancy. It appears to repre- t the first case of myeloma terminating as lymphocytic kemia in which the leukemic cells were not obviously of plasmacytic type. (28 refs.)

5303 **Chronic Lymphocytic Leukemia (CLL) Terminating in Multiple Myeloma: Report of Two ses.** (Eng) Kough, R. H. (Dept. Hematology-Oncology, isinger Medical Center, Danville, PA, 17821); Makary, A. *Blood* 52(3): 532-536; 1978.

e late development of multiple myeloma (MM) in two eld- y patients with chronic lymphocytic leukemia (CLL) is orted. In the first case, an 81-yr-old woman developed nptoms of MM 80 mo after the onset of CLL, and a diag- is of IgAκ MM was made 95 mo after the diagnosis of L. In the second case, a 74-yr-old man developed symp- ns of MM 169 mo after the onset of CLL, and a diagnosis κ light-chain MM was made 192 mo after the diagnosis CLL. Both cases of CLL had responded well to intermit- t low-dose chlorambucil therapy, but the MM failed to pond to cyclic melphalan-prednisone therapy. The finding 2 cases of MM late in the course of CLL among 105 cases CLL reviewed remains unexplained. However, the sugges- n that there is an increased prevalence of MM in CLL is attractive one, because both are B-cell neoplasms and be- se of the increased frequency of asymptomatic monoclon- gammopathies in CLL found by others. (21 refs.)

5304 **Lodgement and Extravasation of Tumour Cells in Blood-Borne Metastasis: An Electron Micro- pe Study.** (Eng) Kinjo, M. (Dept. Pathology, Faculty dicine, Kyushu Univ., 3-1-1 Maidashi, Higashi-ku, kuoka 812, Japan). *Br J Cancer* 38(2): 293-301; 1978.

e lodgement and extravasation of ascites hepatoma cells h high (line AH 130) and low [line AH 130 F(N)] throm- lastic (TP) activities were examined by electron micros- y, and the role of TP activity in blood-borne metastasis determined. Donryu rats were inoculated with 10^7 s/0.2 ml cell suspension of either line and sacrificed im- diately or at times up to 72 hr postinjection. Soon after ction, three types of tumor cell emboli were found in the erioles and capillaries of the lung. Type I, which had rked aggregation of platelets and deposition of fibrin, was mainly seen when AH 130 cells were injected. Detachment and fragmentation of endothelial (ET) cells resulted 1-3 hr later. Type II had loosely aggregated platelets, and type III had no aggregation of platelets or fibrin deposition. Types II and II were mainly seen with AH 130 F(N) cells, and they did not accompany severe structural changes in the ET cells. Tumor cell-platelet complexes appeared to be induced by TP released from tumor cells rather than that from the detached ET cells. At 1-6 hr after infection of AH 130, tumor cells were found beneath the detached ET cells in areas with microthrombi. In places, tumor cells closely adhered to and extended cytoplasmic processes to the ET cells, forming indentations. Some of these processes penetrated through the defects to the subendothelial space, with desquamation of the ET cells. At 3 days, the number of metastatic foci was higher in rats inoculated with AH 130. The results indicate that TP activity is important to microthrombi formation in the lodgement phase and that it might be one of the factors facilitating blood-borne metastasis. When tumor cells had low TP activity, there were no severe structural changes of the ET cells in the entire process from lodgement to extravasation. (20 refs.)

78-5305 **Cutaneous Angiosarcoma of the Hip.** (Eng) Zdrojewski, J. F. (Beaver Medical Clinic, Redlands, CA); Hodge, S. J.; Scheen, S. R.; Owen, L. G.; Smith, S. Z. *South Med J* 71(8): 914-916; 1978.

The case of a 63-yr-old woman who developed a fatal angiosarcoma of the hip approx 10 yr after surgery and intracavitary irradiation (8,000 rads) for a uterine malignancy is reported. The patient was treated by lymph node dissection and cobalt irradiation (5,000 rads) for right inguinal metastases 4 yr after the initial treatment. She then developed aseptic necrosis of both femoral heads, resulting in a right hip replacement procedure with an Austin-Moore prosthesis. The latter was removed after 5 yr because of continuing purulent drainage from the hip incision. Mild chronic lymphedema of the involved lower extremity was noticed after insertion of the prosthesis, and the patient eventually developed a cutaneous angiosarcoma in the affected area. Any or all of these factors might bear a causative relationship to the angiosarcoma, but none can be proved. (27 refs.)

78-5306 **Leiomyomatosis Peritonealis Disseminata. An Ultrastructural Study.** (Eng) Nogales, F. F. (Dept. Pathology, Univ. Seville Medical Sch., Seville, Spain); Matilla, A.; Carrascal, E. *Am J Clin Pathol* 69(4): 452-457; 1978.

A histopathologic study was made of the eighth documented case of leiomyomatosis peritonealis disseminata (LPD), a disease that consists of widespread peritoneal nodules of a leiomyomatous nature that involve the parietal peritoneum and the visceral peritoneum of abdominal organs. Six of the pa-

tients were black women. LPD was discovered upon cesarean section in an asymptomatic 34-yr-old Caucasian woman admitted for delivery. The main proliferative cell type was identified by electron microscopy as a mature leiomyocyte with all its associated ultrastructural features. Intimately intermixed with the leiomyocytes were hybrid cells (myofibroblasts) in which fibroblastic features such as abundant rough endoplasmic reticulum, prominent Golgi complexes, and a resemblance to stromal collagen fibers coexisted with variable amounts of cytoplasmic fibrils and electron-dense bodies. The histogenesis of LPD is considered to be a multicentric metaplastic change determined by an abnormal tissue response to elevated hormone levels associated with pregnancy or ovarian functioning tumors. The cell of origin is suggested to be the multipotent subcelomic mesenchymal cell, which retains the capacity to differentiate into several tissues, among them smooth muscle. The myofibroblasts may represent a transitional morphologic stage between the mesenchymal cell and the smooth muscle proliferating cell. (17 refs)

78-5307 **Malignant Fibrous Histiocytoma. Clinicopathologic and Ultrastructural Study of 12 Cases.** (Eng) Limacher, J. (Dept. Pathology, Hotel-Dieu de Quebec, Quebec City, Quebec G1R 2J6, Canada); Delage, C.; Lagace, R. *Am J Surg Pathol* 2(3): 265-274; 1978.

The light and electron microscopy findings for 12 specimens of malignant fibrous histiocytoma of the soft tissues are presented. The specimens were removed from eight men and four women aged 29-88 yr. All primary lesions were located in the lower extremities except for one in the arm, one in the thoracic wall, and one in the jaw. Nine patients had recurrences and three had metastases. The essential histologic feature of this tumor was its biphasic composition, with both histiocytic and fibroblastic components, the latter showing a characteristic storiform pattern. Furthermore, a variable number of xanthomatous cells and multinucleated giant cells were observed. Ultrastructural studies confirmed the presence of these cells and also revealed the existence of a primitive mesenchymal cell. It is suggested that this mesenchymal cell is a primitive histiocyte from which the two main cellular components of the tumor arise. The precise significance of the xanthomatous cells and the multinucleated giant cells is unknown. The former may represent some sort of terminal state of either main cell line. (23 refs.)

78-5308 **Familial Phaeochromocytoma With von Hippel's Disease in One Sister and Ectopic Adrenal Cortex in the Kidney in Another.** (Eng) Mendelow, A. D. (Medical Sch., Hospital St., Johannesburg 2001, S. Africa); Kay, S.; Levin, E.; Mieny, C. J. *Br J Surg* 65(2): 138-140; 1978.

Two sisters, aged 12 and 20 yr at presentation, developed bilateral adrenal pheochromocytomas. The former had ectopic adrenal cortical tissue and the latter had von Hippel's disease. This is the first known association of the former with familial pheochromocytoma. (7 refs)

78-5309 **Aniridia, Cataracts, and Wilms' Tumor i Monozygous Twins.** (Eng) Cotlier, E. (Dept Ophthalmology and Visual Science, Yale Univ. Sch. Medicine, 333 Cedar St., New Haven, CT, 06510); Rose, M.; Moe S. A. *Am J Ophthalmol* 86(1): 129-132; 1978.

The first instance of aniridia-Wilms' tumor syndrome in mer tally retarded identical twin girls is reported. Both had con genital bilateral aniridia, cataracts, and glaucoma, but onl one developed a Wilms' tumor. It is proposed that a com bined gonadal-somatic cell mutation occurred in the twi with Wilms' tumor and a gonadal mutation occurred in th other twin. A gonadal somatic mutation probably occurre in a Wilms' tumor allele and a pure gonadal mosaicism affec ed the aniridia allele. A two-allele gonadal and a somat mutation could explain the manifestation of the tumor in on one twin. The aniridia-Wilms' syndrome in twins furth documents the relationship of teratogenic malformations an neoplasms. (21 refs.)

78-5310 **Chemodectomas of the Carotid Body an Glomus Tympanicum. Sequential Occurrence i Sisters.** (Eng) Schmidt, F. E. (Dept. Surgery, Tulane Uni Sch. Medicine, 1430 Tulane Ave., New Orleans, LA, 70112 Lewis, M. L.; Kahle, H. R. *JAMA* 240(12): 1266-1267; 197

Two sisters, aged 47 and 44 yr, developed chemodectom of the carotid body 10 and 1.5 yr, respectively, after they we diagnosed with tumors of the glomus tympanicum. No recu rences have been noted in either patient since excision of th chemodectomas, and neither patient has had evidence of co tralateral tumors at either site. (3 refs.)

78-5311 **Extensive Metastases in Peutz-Jeghers Sy drome.** (Eng) Ryo, U. Y. (Div. Nuclear Med cine, Michael Reese Hosp. and Medical Center, 2839 S. El Ave., Chicago, IL, 60616); Roh, S. K.; Balkin, R. B.; Sie band, L. B.; Sobel, G. W.; Pinsky, S. M. *JAMA* 239(21 2268-2269; 1978.

A 27-yr-old woman with Peutz-Jeghers (PJ) syndrome sin age 11 yr was hospitalized with a sudden onset of weakne of the right extremity, expressive aphasia, and a 3 mo histo of back pain. Liver and whole-body scintigrams demonstr ed multiple metastatic disease. Postmortem examinati showed extensive metastases in bone, liver, brain, lung, a

eft ovary. The source of the metastases was a malignant hange from PJ polyps. The incidence of malignant transfornation resulting from PJ polyps is 2%-3%. (4 refs)

8-5312 **Familial Cushing's Syndrome.** (Eng) Arce, B. (Inst. Endocrinology and Metabolic Diseases, Zapata y D, Havana 4, Cuba); Licea, M.; Hung, S.; Padron, R. *Acta Endocrinol (Kbh)* 87(1): 139-147; 1978.

The case reports of four siblings, two women and two men, vith Cushing's syndrome are presented. Their ages at diagnois were 15, 15, 13, and 32 yr, respectively. All four patients vere short in stature and they had a disturbed carbohydrate netabolism. Adenomatous hyperplasia of the adrenal glands vas demonstrated in three patients, and a virilizing adrenal arcinoma was noted in the fourth. A four-generation geneaogical study of both branches of the family revealed no other ase of adrenal hyperfunction. It is suggested that these tunors could have arisen from anomalous ACTH hyperproduction. These cases indicate a possible familial pathogenic rigin of Cushing's syndrome. (3 refs)

8-5313 **Ultrastructural Study of the Normal Mucosa-Adenoma-Cancer Sequence in the Development Familial Polyposis Coli.** (Eng) Mughal, S. (Dept. Histopaology, Westminster Medical Sch., Univ. London, Udall reet Labs., Udall St., London SW1P 2PP, England); Filipe, I. I. *J Natl Cancer Inst* 60(4): 753-768; 1978.

he ultrastructural changes that occur in the mucosae of paents with familial polyposis coli (FPC) were studied. The ithelial atypia were graded on the basis of vesiculation and creasing numbers of electron-dense bodies (EDB) and lysomes in the mature and immature absorptive cells (IAC), e presence of immature and undifferentiated cells, variaons in the goblet cells and the appearance of atypical secrery cells (ASC), and nuclear changes. With Grade 0 atypia, few EDB were noted in the apical region of the mature sorptive cells. With Grades 1 and 2, vesiculation and ineased EDB were noted in mature cells. Goblet cells were ller and sometimes distended with mucus; this distension ay lead to disruption of the theca and leakage of secretory aterial into the adjacent cytoplasm. In Grades 3 and 4, mature and undifferentiated cells appeared at a higher an normal level in the crypt, and IAC and ASC were comon. In Grade 5, the population consisted mainly of immare cells with numerous EDB, ASC were prominent, and clei showed marked pseudostratification. Grades 6 and 7 nsisted mainly of undifferentiated cells, and there was arked nuclear irregularity. Carcinomas contained Grade 7 ithelia and Grades 5 and 6 glandular structures. Specimens m normal mucosa of FPC patients showed ultrastructural anges in 56%. The incidence of both atypia and adenomais polyps was higher on the left side of the colon than on the right side. These findings illustrate the adenoma-carcinoma sequence and support its occurrence. (27 refs)

78-5314 **Polyposis Coli. The Clinical Spectrum in Adults.** (Eng) Cooke, S. A. (Dept. Surgery, Univ. of the Witwatersrand, Johannesburg, S. Africa). *S Afr Med J* 53(12): 454-457; 1978.

The case reports of four patients with polyposis coli are presented to illustrate the unusual features of different types of this disease. The first patient is a 42-yr-old man with no family history of colonic disease who developed metaplastic polyps. The second is a 41-yr-old man with the multiple form of juvenile polyposis coli. The third is a 57-yr-old woman with adenomatous polyposis coli that is thought to have arisen by a spontaneous mutation. The fourth is an 18-yr-old girl who underwent total colectomy; she had had adenomatous polyposis coli at the age of 10, was a member of a family with a known predisposition to polyposis, and had multiple osteomas in the mandible. The types of lesions represented by these cases are discussed. A comparison of the fourth patient with Gardner's syndrome patients suggests that the differences between familial polyposis and Gardner's syndrome may be due only to a variation in the expressivity of the different extracolonic manifestations associated with the polyposis. Furthermore, juvenile polyposis, familial adenomatous polyposis, and carcinoma of the colon may be interrelated because they have occasionally been diagnosed in the same family. (15 refs)

78-5315 **Thymomas in Patients with Myasthenia Gravis.** (Eng) Slater, G. (Dept. Surgery, Mount Sinai Sch. Medicine, Fifth Ave. and 100th St., New York, NY, 10029); Papatestas, A. E.; Genkins, G.; Kornfeld, P.; Horowitz, S. H.; Bender, A. *Ann Surg* 188(2): 171-174; 1978.

Thymoma occurred among 10% of all myasthenia gravis patients seen at one hospital. The histological classification was 72% lymphoepithelial, 24% lymphocytic, and 4% epithelial. Forty-three percent of the thymomas were invasive. (13 refs)

78-5316 **The Formal Pathogenesis of Primary Squamous Epithelial Carcinomas of the Thyroid (Meeting Abstract).** (Ger) Bocker, W. (Hamburg, W. Germany). *Zentralbl Allg Pathol* 122(3): 292; 1978. (no refs)

78-5317 **Multiple Endocrine Adenomatosis: In Support of the Common Origin Theories.** (Eng) Janson, K. L. (Section of Urology, Dept. Anatomy, Tulane Univ.

Sch. Medicine, New Orleans, LA); Roberts, J. A.; Varela, M. *J Urol* 119(2): 161-165; 1978.

A family with features of multiple endocrine adenomatosis types 1 and 2 was studied, and evidence in support of a common etiologic origin of the tumors associated with this syndrome is presented. A 9-yr-old girl (case 1) was found to have a right pheochromocytoma; chromosome study revealed a marker on the 15th chromosomal pair. Her 31-yr-old mother (case 2) had bilateral adrenal pheochromocytomas and an accessory pheochromocytoma in a paraaortic position, a right renal cystadenoma with renal cysts and a left renal adenoma, and three islet cell tumors of the pancreas. Chromosome studies indicated a marker on the 15th chromosomal pair identical to that of her daughter and the same histocompatibility haplotype as her daughter. The mother of case 2 (case 3) had had a pituitary tumor removed at the age of 22 and was later diagnosed as having bilateral pheochromocytomas. Chromosomal analysis of the mother of case 3 (case 4) revealed no markers. A 50-yr-old sister of case 3 has a marker on the 15th chromosomal pair but no adenomatosis. A younger sister and brother of case 1 have this marker but no evidence of disease. These findings suggest a common genetic origin of multiple endocrine adenomatosis but that not all persons with this genetic information develop tumors. (20 refs)

78-5318 **Association of Acromegaly and Meningiomas.** (Eng) Bunick, E. M. (Div. Endocrinology and Metabolism, Hahnemann Medical Coll. and Hosp., 230 N. Broad St., Philadelphia, PA, 19102); Mills, L. C.; Rose, L. I. *JAMA* 240(12): 1267-1268; 1978.

The coexistence of a growth hormone-producing pituitary tumor and a subfrontal meningioma at the time of initial diagnosis in a 57-yr-old man is reported. There are only six similar cases in the literature. In two of these patients the pituitary tumor and the meningioma were present before the initiation of therapy. The other four patients underwent irradiation of the pituitary fossa for treatment of acromegaly before the meningioma developed. The present patient had both tumors without any history of head trauma, infection, or irradiation. There is no way to determine which tumor developed first, and the exact nature of the relationship between acromegaly and meningiomas is not known. (3 refs.)

78-5319 **The Role of the Subependymal Plate in the Origin of Experimental Gliomas: A Sequential Electron Microscope Study (Meeting Abstract).** (Eng) Lantos, P. L. (Middlesex Hosp. Medical Sch., London, England). *J Neuropathol Exp Neurol* 37(5): 647; 1978. (no refs)

78-5320 **Human Neuroblastoma Serially Transplanted in Nude Mice and Metastases.** (Eng) Hata, J. I. (Dept. Pathology, Tokai Univ., Sch. Medicine, Bohseidai, Isehara, Kanagawa, 259-11, Japan); Ueyama, Y.; Tamaoki, N.; Furukawa, T.; Morita, K. *Cancer* 42(2): 468-473; 197

The direct transplantation of a neuroblastoma from 3-yr-old girl into nude BALB/c mice is reported. A metasta ic tumor of the paraaortic lymph node obtained at surge was minced, and the fragments were transplanted sc into t mice; serial transplantation was then established. The histol gy of the transplanted tumor was almost the same as that the original tumor. During serial transplantation, a high fr quency of metastasis to distant sites such as the ovari lymph nodes, and cerebrum was observed; the metastatic ra to the ovaries reached 66%. The distribution of the orga affected by metastasis was similar to that in humans wi neuroblastoma. This transplantable human neuroblasto may be useful for studies of the morphological and biologi nature of these tumors. (7 refs.)

78-5321 **Massive Peripheral Giant-Cell Reparat Granuloma of the Jaw: A Pregnancy Depend Tumor.** (Eng) Caillouette, J. C. (50 Bellefontaine St., Pasa na, CA, 91105); Mattar, N. *Am J Obstet Gynecol* 131(176-179; 1978.

A 21-yr-old pregnant woman had a large giant-cell granu ma that may have been enhanced by the diminished immu response and hormonal changes associated with pregnan The high levels of estrogens and gonadotropic hormones d ing pregnancy have a positive trophic effect on the buc mucosa and augment glycogen deposition in the epitheli Peripheral giant-cell reparative granuloma should not be n taken for true giant-cell tumor, which is rare. (19 refs)

78-5322 **Malignant Transformation of Esopha Columnar Epithelium.** (Eng) Berenson, M. (Div. Gastroenterology, Univ. Medical Center, Salt L City, UT, 84132); Riddell, R. H.; Skinner, D. B.; Fres J. W. *Cancer* 41(2): 554-561; 1978.

The cases of two men (aged 47 and 69 yr) with esopha columnar epithelium (Barrett's esophagus) in which micr vasive adenocarcinoma of the esophagus developed are ported. The former had multiple foci of in situ carcin contiguous with epithelium resembling that of the stom and intestine. The latter had signet-ring type adeno cinoma. The adenocarcinoma appeared to develop dire from the dysplastic epithelium, providing direct evidence the dysplastic process is neoplastic. The origin of esopha columnar epithelim is not known, but it may originate f reflux-induced ulceration and subsequent regeneration by mature gastric cells that undergo metaplastic change. tients with columnar esophageal epithelium should be tinely checked for malignant transformation. (28 refs)

78-5323 **Cylindrical Metaplasia of the Lower Esoph (Meeting Abstract).** (Fre) Ozzello, L. (Ins de pathologie, Universite de Lausanne, Lausanne, Swi

d); Savary, M.; Roethlisberger, B. *Schweiz Med Wo-enschr* 108(13): 506; 1978. (no refs)

-5324 **The Aryl Hydrocarbon Hydroxylase Polymorphism and Respiratory Cancer (Meeting Abact).** (Eng) Paigen, B. (Roswell Park Memorial Inst., Buf-, NY, 14263); Ward, E.; Gurtoo, H. L.; Minowada, J.; ncent, R.; Parker, N. B.; Paigen, K. *Proc Am Assoc Cancer* 19: 100; 1978. (no refs)

-5325 **Histochemical Observations on Nodules Induced in the Mouse Liver by Phenobarbitone.** ng) Butler, W. H. (Pharmaceuticals Div., ICI Ltd., Mere-e, Alderley Park, Macclesfield, Cheshire SK10 4TG, En-nd); Hempsall, V. *J Pathol* 125(3): 155-161; 1978.

eanling C3H mice were fed phenobarbitone in the diet (500 m for 1 wk, followed by 1,000 ppm for the duration of the periment, 2 yr), and their livers were examined histochemi-lly to determine which features are associated with malig-nt neoplasms. A total of 13 livers from phenobarbitone-fed ce and 3 livers from control animals, all with macroscopic dules, were examined. The morphology of the lesions in e treated animals depended on the preparative techniques ed. On examination of hematoxylin and eosin-stained sec-ns, nodules from 11 treated livers showed a simple trabecu-pattern of cells with abundant eosinophilic cytoplasm; dules from the other 2 livers had thickened and irregular abeculae with wide vascular spaces. Examination of paraf-sections indicated that six nodules contained areas show-g a dilated vascular pattern and irregular trabeculae. On rial sectioning, vascular emboli of hepatic cells were ob-rved in the lungs of the two animals with the thickened abeculae. A varying pattern of histochemical reaction was ted. The aniline hydroxylase reaction was dense in the sim-e nodules and centrilobular areas of the treated mice, but was weak in the abnormal trabecular lesions. Tissues from of the nodules in treated mice were transplanted sc into eanling male C3H mice; two successful transplants were corded. These findings suggest that it is possible to predict havioral characteristics of mouse hepatic nodules on the sis of certain morphological characteristics. (12 refs.)

3-5326 **Conglomerative Siderosis and Carcinoma of the Lung.** (Fre) Lemenager, J. (Clinique medicale , C.H.U., 14033 Caen Cedex, France); Wyplatz, J.; Mand-d, J. C.; Chasles, J.; Le Bouffant, L.; Caillard, J. F.; Benard, . *Rev Fr Mal Respir* 6(4): 431-433; 1978.

51-yr-old worker in the metallurgy industry presented with opaque focus in each lung. Thoracotomy revealed a focus conglomerative siderosis in the left lung and an adenocar-noma in the right lung. Histological and mineralogical ex-nination of the siderosis revealed a giant cell granuloma, high iron content, and particles of titanium oxide and silver. ggregates of different minerals were found in the fibrosis surrounding the siderosis. The adenocarcinoma, which was moderately differentiated, contained numerous amphibole asbestos fibers as well as iron oxides, quartz, and traces of silver and feldspar. (3 refs.)

78-5327 **A Histochemical and Ultrastructural Study of Adenocarcinoma of the Lung.** (Eng) Kimula, Y. (Dept. Pathology, Tokyo Metropolitan Inst. Gerontology, 35-2, Sakaecho, Itabashiku, Tokyo 173, Japan). *Am J Surg Pathol* 2(3): 253-264; 1978.

Twenty-five cases of solitary nodular-type adenocarcinoma of the human lung were studied ultrastructurally in an attempt to elucidate the histogenesis of adenocarcinoma at an early and developing stage. Twenty-one cases were type D adenocarcinoma (resembling nonciliated bronchiolar cells), two were type B (resembling the mucous cell of the bronchial gland), one was type A (resembling the bronchial goblet cell), and one was type C (resembling the type II alveolar lining cell). According to criteria of the World Health Organization, 15 lesions were adenocarcinomas and 10 were bronchioloalveolar carcinomas; there were no histochemical or ultrastructural differences between the two. These findings suggest that pulmonary adenocarcinoma may arise from more than one cell type but that the predominant type is apparently from the terminal bronchiolar epithelium. (18 refs.)

78-5328 **Special Features of Intestinal Metaplasia and Its Relation to Early Gastric Carcinoma in Man: Observation by a Method in Which Leucine Aminopeptidase Activity Is Used.** (Eng) Nakahara, K. (Dept. Surgery, Natl. Kyushyu Cancer Center, 595 Minami-Ku, Notame, Fukuoka-City 815, Japan). *J Natl Cancer Inst* 61(3): 693-702; 1978.

A leucine aminopeptidase (LAP) staining procedure was used to determine the degree of intestinal metaplasia and its macroscopic distribution in gastric mucosa in order to investigate the relationship between intestinal metaplasia and gastric carcinoma. LAP is a specific enzyme of intestinal metaplasia, and the area showing a positive reaction for this enzyme corresponded strictly with the zone of intestinal metaplasia examined microscopically. This method was used to examine specimens of gastric carcinoma confined to the mucosa from 40 Japanese patients. Gastric mucosa containing differentiated tubular-type carcinoma (24 cases) was associated with a high degree of metaplasia, but a low degree of metaplasia was found in the 16 cases of poorly differentiated carcinoma. The more differentiated a tubular-type carcinoma was, the more closely it was related to intestinal metaplasia. In contrast, all carcinomas arising from the mucosa without intestinal metaplasia (18%) were poorly differentiated. Therefore, gastric carcinomas occurring in Japanese patients are frequently and closely related to intestinal metaplasia. (32 refs.)

78-5329 **Cancer of the Stomach after Resection for Peptic Ulcer.** (Rus) Patiutko, Iu. I. (Dept. Oncology, I. M. Sechenov First Medical Inst., Moscow, USSR). *Khirurgiia (Mosk)* (3): 27-31; 1978.

To evaluate whether resection of the stomach for peptic ulcer increases the relative risk of cancer in the remaining part of the stomach, the case histories of 942 patients with gastric ulcer treated surgically between 1946 and 1952 were subjected to retrospective analysis. Nineteen patients had developed cancer of the gastric stump: 1 within 6-10 yr of surgery, 3 within 11-15 yr, 3 within 16-20 yr, 7 within 21-25 yr, and 5 > 26 yr postsurgery. Calculation of the expected age-predicted incidence of cancer of the proximal region of the stomach (patients had undergone resection of distal region) showed that observed and expected values were in good agreement only within the first 10 yr after resection; 21-25 yr later the observed incidence was 3.5 times greater and > 25 yr later it was 12.5 times greater than expected. (11 refs)

78-5330 **Pathogenesis of Gastric Cancer in Pernicious Anemia.** (Eng) Ruddell, W. S. (Dept. Gastroenterology, Central Middlesex Hosp., London NW10 7NS, England); Bone, E. S.; Hill, M. J.; Walters, C. L. *Lancet* 1(8063): 521-523; 1978.

Thirteen patients with pernicious anemia (PA) and 13 age-matched controls were studied to determine if nitrite concentrations in the PA patients could be involved in the pathogenesis of gastric cancer. The gastric juice of the PA patients had significantly higher nitrite concentrations, total bacterial counts, and counts of bacteria showing nitrate-reductase activity than the gastric juice of the controls. The results of an in vitro nitrosation experiment indicated that appreciable quantities of nitrosamines were detected in extracts of gastric juice from the PA patients. Nitrosamines were not detected in any of the extracts from the control experiments without added nitrite. If similar nitrosation occurs in vivo, the intragastric production of carcinogenic N-nitroso compounds could explain the high incidence of gastric cancer in patients with PA. (17 refs)

78-5331 **Squamous Cell Carcinoma of the Stomach.** (Eng) Won, O. H. (1221 Mowry St., Old Forge, PA, 18518); Farman, J.; Krishnan, M. N.; Iyer, S. K.; Vuletin, J. C. *Am J Gastroenterol* 69(5): 594-598; 1978.

The case report of a 55-yr-old woman with a pure squamous cell carcinoma of the stomach is given. The tumor arose in an area lined by squamous mucosa continuous with that of the esophagus, but located well within the stomach. It is thought that this squamous mucosa was present congenitally and that it progressed through dysplasia to neoplasia and invasive cancer. (21 refs.)

78-5332 **Frequency of Primary Liver Carcinoma A sociated by Cirrhosis of the Liver at Cipto Ma gunkusumo Central Hospital, Jakarta; Assessed by Pe toneoscopy (Meeting Abstract).** (Eng) Akbar, N. (D Hepathology Medical Faculty, Univ. Indonesia, Jakarta, I donesia); Lesmana, L.; Sulaiman, A.; Noer, A. M.; Sukato U. *In: Summary Program and Abstracts of Papers. Proce ings of the 3rd Asian Cancer Conference Held by the Phil pine Cancer Society under the Auspices of the Asian Federat of Organizations for Cancer Research and Control in Mani 26-30 September, 1977.* Philippine Cancer Society. (Mani Philippines): 184 pp.; 35-36; 1977. (no refs)

78-5333 **Familial Liver-Cell Adenomas and Diabe Mellitus.** (Eng) Foster, J. H. (Dept. Surge Hartford Hosp., Hartford, CT, 06115); Donohue, T. A.; B man, M. M. *N Engl J Med* 299(5): 239-241; 1978.

A family was encountered in which four members, 43-yr-old mother, two daughters aged 17 and 18 yr, and 15-yr-old son, had liver cell adenomas. All were diabetic, a the two daughters also had sclerocystic ovaries, suggestive a change in their internal hormonal milieu. Liver-functi tests gave normal results in all, except for elevated enzym in one daughter (presumably related to an acute episode hemorrhagic necrosis), and a twice-normal elevation of al line phosphatase in the son. A fourth child, a 12-yr-old n diabetic girl, was not affected. The mother's father, also diabetic, died with diffuse pulmonary metastases from autopsy-confirmed hepatocellular carcinoma occurring i cirrhotic liver. His nondiabetic father had died with bi sy-confirmed hepatocellular carcinoma in a cirrhotic liv There are no reports of an association of diabetes melli (DM) with benign or malignant liver tumors. The mild ture and strong family penetrance of DM in this family s gest that the diabetic phenotype is that of maturity-onset d betes of the young as opposed to classic juvenile-on diabetes. This apparent autosomal dominant inheritance DM may correlate with a higher incidence of liver cell ade mas in other families with similar diabetic phenotypes. I hypothesized that a change in the hormonal mil caused by endogenous or exogenous sex steroids, masks a fundamental, perhaps hereditary, defect in bohydrate metabolism, resulting in nodule forma in the liver. (10 refs)

78-5334 **Evaluation of Hepatocellular Neoplasms Mice.** (Eng) Ward, J. M. (Tumor Pathol Branch, Carcinogenesis Testing Program, NCI, NIH, Pu Health Service, US Dept. Health, Education, and Welf Bethesda, MD, 20014); Vlahakis, G. *J Natl Cancer Inst* 61 807-811; 1978.

The genesis of hepatocellular neoplasms was studied in C3H-A*vy*fB male mice, a strain with a high incidence of n

y occurring hepatocellular tumors. At 3, 6, 9, 12, and 15 of age, preselected groups of six mice were killed and a nplete necropsy was performed. The number of mice with nors in these age groups was 0%, 33.3%, 50%, 66.7% and 3%, respectively. As the mice aged, the number of tumors liver and the mean diameter of the tumors increased. tologically, the smallest tumors were composed of sheets ells and were better differentiated than the largest tumors. all foci of hepatocytes in prominent trabeculae were seen a few small tumors, but prominent trabecular formation a common characteristic of large tumors. Metastatic tu-rs in these mice plus those in C3HfC, C3H, C3HfB, HfB x YBR)F_1, and C57BL/6 mice were studied morpho-ically. The pulmonary metastases were composed of a l-differentiated sheet of hepatocytes that resembled those he solid liver tumors. The smallest hepatocellular neo-sms appeared to represent early stages in the development netastatic hepatocellular carcinoma. (12 refs.)

5335 **Vaginal Metastasis from Renal Cell Carcinoma: Routes of Metastasis.** (Jpn) Masuda, F. (Dept. ology, Jikei Univ. Sch. Medicine, Tokyo, Japan); Hi-numa, H.; Saski, T.; Arai, Y.; Shoji, R.; Teramoto, K.; nagisawa, M.; Chen, Z.; Machida, T. *Jpn J Urol* 69(4): -479; 1978.

eft renal cell carcinoma was diagnosed in a 22-yr-old wom-Renal venography revealed a tumor embolism from the al vein to the inferior vena cava, and a chest x-ray indicat-metastasis to the bilateral lymph nodes. Five months later, patient developed vaginal bleeding. One small tumor was nd near the vaginal introitus and another at the left vagi-wall adjacent to the uterine neck. Histological examina-n of the vaginal lesions showed a clear cell adenocarcinoma he capillaries, confirming the presence of metastases from renal lesion. The possible routes of metastasis were stud-in adult mongrel dogs by following the circulation of the ovarian vein before and after ligation of the left renal vein. e results suggest that renal cell carcinomas metastasize to vagina as follows: in a left renal cell carcinoma, the tumor ls flow from the renal vein, directly or through the ureteral n, to the left ovarian vein, the ovarian plexus, the rovaginal plexus, and the vagina. In the case of a right al cell carcinoma, the tumor cells flow from the renal cap-ar veins or the ureteral vein to the vagina through the right rian vein. (13 refs)

-5336 **Functional and Morphological Studies of Human Renal Cell Carcinoma Using a Nude Mouse l Cell Culture System.** (Jpn) Katsuoka, Y. (Dept. Urology, n. Med., Keio Univ., Keio, Japan). *Jpn J Urol* 69(3): 5-303; 1978.

irty-six surgical specimens of human renal cell carcinoma obtained over a 5-yr period were cultured, transplanted into nude mice, and analyzed with respect to their functional and morphological characteristics. Eleven primary cultures, 2 continuous cultures, and 6/12 tumor transplants were successful, and 4/6 transplanted tumors are still growing. Among the latter is a tumor capable of producing erythropoietin (EP) and derived from metastatic foci in a lung. Histopathologically, the transplanted tumors, the continuous cultures, and the original tumors were basically identical. Indirect culture through a nude mouse produced a cell line (KU-2) whose histopathological characteristics remained unchanged even after it was transplanted back into a nude mouse. There were brush border-type structures in the transplanted tumors and radially arranged microvilli on the culture cells (as shown by electron microscopy), proof that renal cell carcinoma originates in a proximal tubular cell. The transfer of erythrocytosis to the tumor-bearing mice and the determination of EP activity in the tumor tissue raise the possibility that the tumor per se is capable of producing EP. The development of hepatomegaly in the tumor bearers, plus the other findings, may explain the unique functional characteristics of these tumors. (82 refs)

78-5337 **Cancer Risk with Different Types of Gallstones.** (Ger) Grosse, H. (Bezirkskrankenhaus-Prosektur, Billrothstrasse 22, DDR-23 Stralsund, E. Germany). *Arch Geschwulstforsch* 47(8): 710-718; 1977.

The association between gallstones and different types of cancer was investigated in 22,868 autopsied adults. Of these, 7,411 had cholelithiasis or had undergone cholecystectomy. In cancerous gallbladders, multiple faceted stones and solitary combined stones were seen most frequently; pigmented stones, pure crystalline cholesterol stones, and lobulated stones were rarely seen. As the partial volume of gallstones increased, so did the number of cases of cholecystitis and carcinoma. In men with all forms of gallstones, carcinomas of the lung, stomach, colon, rectum, and prostate gland were more common than gallbladder carcinoma. In women with multiple faceted stones, the most frequent cancer was that of the gallbladder. The area of the gallbladder affected by the stones was more important to the localization of a later carcinoma in women than in men. The percentage of unoperated patients with gallstones who later developed any type of cancer was not higher than that of patients with a previous cystectomy. (42 refs)

78-5338 **A New Aspect of the Urinary Excretion of Tryptophan Metabolites in Patients with Cancer of the Bladder.** (Eng) Teulings, F. A. (Dept. Biochemistry, Rotterdamsch Radio-Therapeutisch Instituut, P.O. Box 5201, 3075 EA Rotterdam, Netherlands); Peters, H. A.; Hop,

W. C.; Fokkens, W.; Haije, W. G.; Portengen, H.; van der Werf-Messing, B. *Int J Cancer* 21(2): 140-146; 1978.

Excretion of tryptophan metabolites was examined in 165 urine samples obtained from bladder cancer patients (67), renal cancer patients (19), patients cured of bladder cancer (37), and control subjects (40). The metabolites kynurenine, kynurenic acid, 3-hydroxykynurenine, xanthurenic acid, and 3-hydroxyanthranilic acid were separated by ion-exchange chromatography followed by thin-layer chromatography on cellulose. Their concentration was determined by measuring the fluorescent intensity of the spots on the cellulose plates. Thirty-six percent of the bladder cancer patients and 67% of the renal carcinoma patients excreted abnormally high amounts of at least one of the metabolites, most frequently 3-hydroxyanthranilic acid, 3-hydroxykynurenine, and kynurenine. In bladder cancer an elevated excretion of metabolites occurred principally in patients with obstruction to the outflow of urine from the kidneys. Ureteral obstruction, probably a direct consequence of the presence of tumor in the urinary tract, causes an alteration in renal function that is reflected in urea and creatinine retention. The high incidence of abnormal excretion of tryptophan metabolites in renal cancer also points to alterations in renal function caused by the tumor. These observations do not support the hypothesis that tryptophan metabolites play a part in the etiology of bladder cancer, since raised basal urinary levels of these metabolites are a result, rather than a cause of the disease. (19 refs)

78-5339 **Blue Nevus of the Endocervix: Report of Two Cases and Ultrastructure.** (Eng) Diaz de Molnar, A. M. (Dept. Pathology, Jewish General Hosp., 3755 Cote St. Catherine Road, Montreal, Quebec H3T 1E2, Canada); Guralnick, M.; Ferenczy, A. *Gynecol Oncol* 6(4): 373-382; 1978.

Examination of the surgical specimens from two women, aged 44 and 58 yr, who had undergone hysterectomy for menorrhagia revealed blue nevus lesions in each. The younger woman had a solitary 4- x 4-mm lesion in the posterior one-third of the endocervical canal. In the older women, multiple nevi, the largest measuring 2 x 1.5 cm in diameter, were noted in the upper two-thirds of the endocervical canal. Electron microscopy of specimens removed from the older woman showed that the cells were engaged in melanogenesis similar in all respects to that observed in blue nevus cells of the dermis. Their ultrastructural resemblance and close location to perineurial fibroblasts of nonmyelinated nerve bundles suggest that at least in some instances, the perineural fibroblasts may be the most immediate neural crest precursors of blue nevus cells of the endocervix. The light microscopic appearance of the lesions is also outlined. (19 refs.)

78-5340 **The Histogenetic Significance of Dysplastic Lesions of the Cervix.** (Fre) Hoang-Ngoc Minh (Service Central d'Anatomie et Cytologie Pathologiques C.H.U. F 80000 Amiens, France); Smadja, A.; Orcel, L. *Gynecol Obstet Biol Reprod (Paris)* 7(3): 387-398; 1978.

The results of morphological studies of dysplastic lesions o the uterine cervix are described. These lesions appear to de velop from the vestigial cells that are situated at the endoe ocervical junction. The dysplasias consist of cells with a basc philic cytoplasm and nondistinctive edges. The cells for streams that run from the external os of the cervix towar the endocervix, where they replace and disturb the columna epithelium. These lesions may take one of two forms, regula or irregular, according to the degree of nuclear-cytoplasm disharmony. The slow and insidious evolution of these lesion must be distinguished from dystrophic endocervical lesion that result from a disturbance in tissue nutrition and fro exocervical lesions that can undergo atypical scarring. (refs.)

78-5341 **Genital Infections and Cervical Carcinom (Letter to Editor).** (Eng) Astedt, B. (Dept. Ob stetrics and Gynecology, Malmo Allmanna Sjukhus, Malmo Sweden); Furgyik, S.; Hansson, H. *Br Med J* 2(6131 201-202; 1978.

A link between genital infection with neisseria and cervica cancer is proposed. Of 162 patients infected with neisseri 34 had cervical carcinoma (20% incidence, vs 5% i age-matched controls). The results agree with the opinio that genital infections predispose to cervical neoplasia. (refs)

78-5342 **Endometrial Carcinoma in Gonadal Dysgenes with and Without Estrogen Therapy.** (Eng) C tor, A. G. (Dept. Pathology, Royal Women's Hosp., 7 Swanston St., Carlton, Victoria, 3053, Australia); Fortun D. W.; Evans, J. H.; Kneale, B. L. *Gynecol Oncol* 6(316-327; 1978.

The case reports of two women, aged 29 and 21 yr, who h gonadal dysgenesis and who subsequently developed e dometrial carcinoma are presented. The former was initial seen because of menorrhagia; both initial and recurrent ep sodes were treated by curettage. One of these curettages r vealed Grade 1 adenocarcinoma. Chromosomal analysis r vealed that 80% of the cells had a 45,X constitution and 20 had a 47,XXX constitution. She had never received estrog therapy. The second patient was also initially seen becau of menorrhagia, and she was treated by curettage and lat by estrogen therapy. One year later, regular withdraw bleeding was produced by cyclic progestogen therapy onl During the next 2 yr, she was treated with an estr gen-progestogen preparation; the total amount of estrog she received was estimated to be 15 mg. A curettage duri this estrogen therapy period revealed well-differentiat

rade 1 adenocarcinoma. Chromosome analysis revealed at 56% of the cells had a 45,X constitution, 44% a 46,XXr nstitution. Autoradiography revealed that the ring romosome was a late replicating X chromosome. Both pa-nts were surgically treated and are alive 13 and 7 yr, respec-vely, after surgery. It is suggested that the carcinomas deve-ped because of unopposed endogenous estrogen secretion sulting from anovulation, but a genetic disposition to can-r in gonadal dysgenesis patients cannot be excluded. (24 fs.)

3-5343 **Carcinoma in a Nipple Preserved by Heterotopic Auto-implantation.** (Eng) Allison, A. B. (Oxrd-Lafayette County Hosp., Oxford, MS); Howorth, M. B. *Engl J Med* 298(20): 1132; 1978.

n infiltrating lobular breast carcinoma, with metastasis entified in two lymph nodes, was removed from a 40-yr-old oman by modified radical mastectomy, and the nipple was ansplanted to her groin to preserve it for breast reconstruc-on. Carcinoma was present in sections taken from beneath e nipple. Upon removal of the nipple at the patient's request 1 yr later, pathological examination revealed carcinoma in the nipple. It is not known whether the cancer was already present or developed after transplantation. (2 refs)

78-5344 **Cancer by County: Etiologic Implications.** (Eng) Blot, W. J. (Environmental Epidemiology Branch, NCI, Bethesda, MD, 20014); Mason, T. J.; Hoover, R.; Fraumeni, J. F. *In: Incidence of Cancer in Humans, Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A.; eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4, 602 pp.; 21-32; 1977.

Lung, colon, and oral and pharyngeal cancer incidence was determined in various counties throughout the US, and the results were correlated with those of analytical field studies. In white men, lung cancer mortality was elevated in the Northeast and around large metropolitan areas, but the highest rates were clustered in contiguous counties along the Gulf of Mexico and the Southeast Atlantic coast. Rates among women were high in urban areas. In general, rates were lowest in farming areas; mortality was inversely correlated with county education levels. Mortality among white men was elevated in counties with paper, chemical, and petroleum manufacturing industries. Geographic patterns for colon cancer mortality were identical for men and women. For both sexes and among races, high rates were present throughout the Northeast and low rates were present throughout the South. High mortality rates were associated with urbanization, income, and ethnicity (Irish, German, Czechoslovakian). Colon cancer did not appear to be associated with dietary habits. High mortality from oral cancer among white men predominated in the Northeast, while high rates in white women were clustered in the Southeast. The northern excess among men was attributed to urbanization, tobacco smoking, and alcohol consumption. It is suspected that the po use of snuff among southern women accounts for their excess of oral cancer. Among men, oral cancer mortality was elevated in counties with leather industries, particularly in the central US. Other findings include high skin cancer rates in the South, high bladder cancer rates in men in industrial areas, high stomach cancer rates in Northern European and Spanish American ethnic groups, and rectal cancer rates paralleling those of colon cancer. Studies of cancer mortality in counties grouped according to specific environmental variables are reviewed. (31 refs)

78-5345 **Minimum Incidence Rate Based on Microscopically Diagnosed Cancer in the Semarang City Population. 1970-1974 (Meeting Abstract).** (Eng) Tirtosugondo (Dept. Pathology, Kariadi Hosp., Semarang, Indonesia); Soetoto, H. J.; Brotosaputro, B.; Widagdo, L. *In: Summary Program and Abstracts of Papers. Proceedings of the 3rd Asian Cancer Conference Held by the Philippine Cancer Society under the Auspices of the Asian Federation of Organizations for Cancer Research and Control in Manila, 26 September, 1977.* Philippine Cancer Society. (Manila, Philippines): 184 pp.; 101-103; 1977. (no refs)

78-5346 **Cancer Statistics of Sabah (Meeting Abstra** (Eng) Kulkarni, M. G. (Queen Elizabeth Ho Kota Kinabalu, Sabah, Malaysia). *In: Summary Progr and Abstracts of Papers. Proceedings of the 3rd Asian Ca Conference Held by the Philippine Cancer Society under Auspices of the Asian Federation of Organizations for Ca Research and Control in Manila, 26-30 September, 1977.* P ippine Cancer Society. (Manila, Philippines): 184 pp.; 83- 1977. (no refs)

78-5347 **Cancer Pattern Among Filipino Populatio Hawaii (Meeting Abstract).** (Eng) Hirohata (Biomedical Sciences D-102, Univ. Hawaii, Honolulu, 96822); Kolonel, L.; Nomura, A.; Burch, T. *In: Summ Program and Abstracts of Papers. Proceedings of the 3rd A Cancer Conference Held by the Philippine Cancer Society der the Auspices of the Asian Federation of Organizations Cancer Research and Control in Manila, 26-30 Septem 1977.* Philippine Cancer Society. (Manila, Philippines): pp.; 80-81; 1977. (no refs)

78-5348 **Recent Changes in Estimated Cancer Morta** (Eng) Chiazze, L. (Div. Biostatistics Epidemiology, Dept. Community Medicine and Internat al Health, Georgetown Univ. Sch. Medicine, Washing DC, 20007); Levin, D.L.; Silverman, D. T. *In: Incidenc Cancer in Humans. Proceedings of the Cold Spring Ha Conferences on Cell Proliferation.* Hiatt, H. H.; Watso D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Sp Harbor Laboratory): Origins of Human Cancer. Vol. 4, pp.; 33-44; 1977.

Statistical problems involved in calculating recent change estimated cancer mortality are outlined, and appropr methods for examining these changes are discussed. A c parison of cancer mortality data for 1974 with the most cent provisional 12-mo data for 1975 reveals that there a 2.3% increase in the crude mortality rate and a 0.7% crease in the mortality rate adjusted to the 1940 populat

) the 1940 population. This 0.7% increase contrasts with the 2% av annual increase observed in the final data from 1968) 1974. The appropriateness of extrapolating from ıort-term monthly trends to determine recent changes in ıncer mortality is questioned. However, there appears to be ome increase in cancer mortality from 1974 to 1975, al- ıough not of the magnitude originally reported. Most of the ıcrease appears to be due to respiratory cancer, particularly mong white women. Lung cancer morality rates have been ıcreasing for several years, but mortality rates for cervical nd stomach cancer have been declining at a significant rate. 'he use of age-, race-, sex-, and site-specific final mortality ata for determining changes in cancer mortality removes ome of the confusion in discerning observed changes and ıay provide clues to the etiologies of these changes. (9 refs)

78-5349 **The Relationship of Serum Vitamin A and Serum Cholesterol to the Incidence of Cancer n Evans County, Georgia.** (Eng) Kark, J. D. (Univ. North Carolina, Chapel Hill, NC, 27514). *Diss Abstr Int B* 39(1): 178B; 1978. (no refs)

78-5350 **Environment and Cancer Epidemiology.** (Ger) Friedl, H. P. (Institut fur Krebsforschung, Universitat Wien, Borschkegasse 8a, A-1090 Vienna, Austria). *Oesterr Z Onkol* 4(2-3): 46-52; 1977.

Cancer mortality rates in Austria were analyzed in view of the contention that environmental factors influence the development of at least 80% of all cancers. The mortality rates for the most common malignancies were similar to those in other western industrialized countries. A relationship between cancer risk and the size of the Austrian communities was demonstrated. Compared with other common cancer sites, cancer of the stomach was most common in small communities with mainly an agricultural population. Etiological hypotheses about the origin of stomach cancer are discussed with regard to epidemiological findings and the dietary habits of the population. (13 refs.)

78-5351 **Correlation of Sites.** (Eng) Clemmesen, J. (Danish Cancer Registry, Finsen Inst., Copenhagen 2100, Denmark). *In: Incidence of Cancer in Humans. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4, 602 pp.; 87-100; 1977.

Patterns in the occurrence of malignant neoplasms in Denmark during the period 1943 through 1972 (data obtained from the Danish Cancer Registry) were analyzed. Although there was a considerable regularity in the patterns over the years, there were some outstanding changes: morbidity rates for cancers of the male digestive organs, particularly the stomach, have decreased, as has that for esophageal cancer; cancers of the pancreas, respiratory tract and lung, genitals (especially in men), breast (women only), urinary tract, skin, and hemopoietic system have increased. A socioeconomic grading for lung cancer among men and for cervical uterine cancer is unfavorable to the poor. Age-adjusted mortality rates showed a definite correlation between cigarette consumption and lung cancer and a less pronounced correlation between cigarette consumption and bladder cancer. The ratio of lung to bladder cancer in Denmark, Sweden, Norway, and the US was approx 3:1, whereas the ratios for Britain and Finland were considerably higher. There was no negative correlation between the morbidity rates for cervical and breast cancers in several countries, but reverse ratios appeared in Israel and Japan. (14 refs.)

78-5352 **Regularly Used Drugs and Cancer.** (Eng) Jick, H. (Dept. Medicine, Boston Univ. Sch. Medicine, Boston, MA, 02118); Smith, P. G. *In: Incidence of Cancer in Humans. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4, 602 pp.; 389-398; 1977.

The possible role of the aggregate of all drugs taken on a regular basis on the induction of cancer was studied based on 800 cancer patients and 3,443 comparison patients whose reasons for entering the hospital were thought to be such that their use of drugs on a regular basis would be similar to that of the cancer patients. In the 3 mo prior to hospitalization, 444 of the cancer patients and 1,710 of the comparison patients reported using one or more drugs at least once a week. When examined by age, the proportion of regular users of one or more drugs was similar in both patient groups. When determined for each age-sex stratum separately, the risk ratio estimates associated with regular use of one or more drugs were also similar for the cancer and comparison patients. The upper limit on the proportion of all cancers attributable to regular drug use, in both regular drug users and nonusers, was estimated to be about 1%. Among long-term (5 yr or more) users, the proportion of all cancers that may be associated with long-term drug use was about 2%. Thus, regular usage of drugs accounts for, at most, only a small fraction of all new cases of cancer diagnosed between the ages of 20 and 75 yr. (11 refs.)

78-5353 **Effects of Drugs--Immunosuppression.** (Eng) Hoover, R. (NCI, Bethesda, MD, 20014). *In: Incidence of Cancer in Humans. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold

Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4, 602 pp.; 369-379; 1977.

The risks of various types of malignancy in renal transplant recipients were studied based on data from 16,290 patients who received transplants between 1951 and 1975. Expected risks for the general population were established from the Connecticut Cancer Registry. Eleven patients for which there was evidence that tumors had been transplanted from the donor along with the kidney were excluded. The risk of lymphoma among transplant recipients was 1.5/1,000 patients/yr, or about 19 times that in the general population. This excess was due almost exclusively to a risk of reticulum cell sarcoma, which was approx 150 times greater than expected. Fifty percent of the lymphomas were localized to the brain. The risk of other cancers was about twice that expected, the excess being attributable to increases in soft-tissue sarcomas, adenocarcinomas of the lung, primary liver and bile duct tumors, lower urinary tract cancers, thyroid cancers, and, perhaps, cancers of the uterine cervix. No excesses were noted for cancers of the stomach, colon and rectum, or breast. The relative risk of lymphoma was increased to 16-fold within the year following transplant and thereafter, whereas the increased risk of other cancers appeared 2 yr after transplant and increased progressively thereafter. The risk of cancer seemed to be particularly excessive among those aged <20 yr at transplantation. The implications of these data for several hypothesized mechanisms of carcinogenesis are discussed. (21 refs.)

78-5354 **Estimates of the Cancer Risk Due to Nuclear Electric Power Generation.** (Eng) Ellett, W. H. (Office Radiation Programs, Environmental Protection Agency, Washington, DC, 20460); Richardson, A. C. *In: Incidence of Cancer in Humans. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4, 602 pp.; 511-527; 1977.

The risk of fatal cancer associated with the annual production of one gigawatt (1,000 megawatts) of nuclear electric power was estimated. The estimated number of cancer fatalities due to the extraction and fabrication of uranium fuel was about 0.5/gigawatt-year [GW(e)-y, the amount of energy produced annually by a single nuclear reactor of the type and size currently being constructed]. The estimated number of cancer fatalities due to the reprocessing of spent fuel was about 0.3/GW(e)-y, and the estimated number of fatal cancers due to nuclear reactor effluents was about 0.1/GW(e)-y. The estimated number due to occupational exposure was 0.2/GW(e)-y, and that due to the accidental release of nuclear material was about 0.1/GW(e)-y. The latter estimate was uncertain because fatalities related to non-core-related accidents, fuel reprocessing, and waste storage could not be estimated. In total, about 1.2 cancer deaths could be associated with each gigawatt-year of electrical energy produced. (3 refs.)

78-5355 **Estrogen Use and Cancer of the Uterine Corpu in Alberta.** (Eng) Wigle, D. T. (Bureau Epidem ology, Room 230A, Lab. Centre Disease Control, Ottaw Ontario K1A 0L2, Canada); Grace, M.; Smith, E. S. *Ca Med Assoc J* 118(10): 1279-1280; 1978.

Persons first attending cancer clinics in Alberta, Canada, b tween 1971 and 1973 were interviewed to determine whethe the risk of cancer of the uterine corpus (CUC) was increase among women with a history of estrogen therapy. Two hu dred and two women aged 55 to 74 yr with histological confirmed CUC were compared with 1,243 55- to-74-yr-ol women with primary cancers other than cancer of the breas cervix, uterus, ovary, or other female genital organs. Estroge use was reported by 47.2% of the women in the case grou and by 26.3% of the comparison subjects. Use of estroge for at least 5 yr was reported by 23.9% of the users in th case group and 5.5% of the users in the comparison grou Women who had used estrogens at some time were at a si nificantly higher relative risk of CUC than were women wh had never used estrogens, and the risk was higher for curre users than for former users. The risk increased as the duratio of hormone use increased, and it was especially high amon women who reported use for ≥ 5 yr. About 24% of the CU cases may have been due to current or past use of estrogen The rate of increased incidence over time among women Alberta and Saskatchewan was substantially greater for th age group 55 to 74 yr than for the age group 35 to 54 yr. Th data suggest that the use of estrogens for the treatment menopause-related symptoms should be reconsidered. (refs)

78-5356 **Adenocarcinoma of Cervix Uteri (Meeting A stract).** (Eng) Boonyanit, S. (Dept. Obstetri and Gynecology, Mahidol Univ., Sirriaj Hosp., Bangko Thailand). *In: Summary Program and Abstracts of Pape Proceedings of the 3rd Asian Cancer Conference Held by t Philippine Cancer Society under the Auspices of the Asian Fe eration of Organizations for Cancer Research and Control Manila, 26-30 September, 1977.* Philippine Cancer Societ (Manila, Philippines): 184 pp.; 79-80; 1977. (no refs)

78-5357 **Epidemiologic Features of Canine Ovarian Ne plasms.** (Eng) Hayes, H. M. (Environment Epidemiology Branch, NCI, Bethesda, MD, 20014); Your J. L. *Gynecol Oncol* 6(4): 348-353; 1978.

The epidemiologic features of histologically confirmed ova

neoplasms diagnosed in 94 dogs seen by 13 North erican veterinary university hospitals and clinics 1 March 1974 through June 1976 are described. n classified by cell type or origin, epithelial tumors esented 60% of the case series and granulosa-theca tumors, 27%. Malignant tumors predominated 26, excluding those of mesenchymal and unknown in. The risk of epithelial ovarian neoplasms in- sed strikingly with age, but the risk of granulosa-theca tumors was constant through middle age. Pointer breed s had a statistically significant risk of epithelial ovarian ors, and English Bulldogs had a significant risk of ulosa-theca cell tumors. Mongrel dogs were significantly ed from malignant tumors, but they had about the same as purebreeds for benign ovarian tumors. The epidemi- ic features of ovarian neoplasia in dogs appeared similar eatures noted in women. (21 refs.)

5358 **Faecal Bile Acids and *Clostridia* in the Aetiology of Colorectal and Breast Cancer (Meeting tract).** (Eng) Blackwood, A. (Dept. Clinical Oncology, stern Infirmary, Glasgow, Scotland); Murray, W. R.; ckay, C.; Calman, K. C. *Br J Cancer* 38(1): 175; 1978. (2)

5359 **Breast Cancer in Thailand (Meeting Abstract).** (Eng) Sa-Ngobwarchar, P. (National Cancer t., Bangkok, Thailand); Tangthatswasd, K.; Sontipong, S. *Summary Program and Abstracts of Papers. Proceedings the 3rd Asian Cancer Conference Held by the Philippine ncer Society under the Auspices of the Asian Federation of ganizations for Cancer Research and Control in Manila, -30 September, 1977.* Philippine Cancer Society. (Manila, ilippines): 184 pp.; 25-26; 1977. (no refs)

-5360 **Case-Control Study of Genetic Admixture and Breast Cancer in American Black Women eeting Abstract).** (Eng) Petrakis, N. L. (G. W. Hooper undation, Univ. California, San Francisco, CA, 94143); ipuy, M. E.; Wong, R.; King, M. C. *In: Summary Program d Abstracts of Papers. Proceedings of the 3rd Asian Cancer nference Held by the Philippine Cancer Society under the spices of the Asian Federation of Organizations for Cancer search and Control in Manila, 26-30 September, 1977.* Phil- ine Cancer Society. (Manila, Philippines): 184 pp.; 24; 77. (no refs)

-5361 **An Epidemiological Investigation of Cancer of Cervix in Thailand (Meeting Abstract).** (Eng) onyanit, S. (Dept. Obstetrics and Gynecology, Siriraj Hosp., Mahidol Univ., Bangkok, Thailand). *In: Summary Program and Abstracts of Papers. Proceedings of the 3rd Asian Cancer Conference Held by the Philippine Cancer Society under the Auspices of the Asian Federation of Organizations for Cancer Research and Control in Manila, 26-30 September, 1977.* Philippine Cancer Society. (Manila, Philippines): 184 pp.; 28; 1977. (no refs)

78-5362 **The Replacement Hormone Use and Breast Cancer (Meeting Abstract).** (Eng) Choi, N. W. (Univ. Manitoba, Winnipeg R3E OW3, Canada); Nelson, N. A.; Shalev, C.; Abu Zeid, H. A. *Am J Epidemiol* 108(3): 230; 1978. (no refs)

78-5363 **Evidence Against the Association of Breast Cancer and DES Exposure (Meeting Abstract).** (Eng) Brian, D. (Mayo Clinic, Rochester, MN, 55901); Tilley, B.; Labarthe, D.; O'Fallon, W. M.; Noller, K. *Am J Epidemiol* 108(3): 230; 1978. (no refs)

78-5364 **Genetic Epidemiology of Families with High Incidence of Breast Cancer (Meeting Abstract).** (Eng) King, M. C. (Univ. California, Berkeley, CA, 94720); Elston, R. C.; Lynch, H. T. *Am J Epidemiol* 108(3): 230-231; 1978. (no refs)

78-5365 **Breast Cancer in Young Women: The Effect of Prior Pregnancy (Meeting Abstract).** (Eng) Janerich, D. T. (New York State Dept. Health, Albany, NY, 12237); Flink, E. M.; Glebatis, D. *Am J Epidemiol* 108(3): 235; 1978. (no refs)

78-5366 **Hypothesis on Relationship Between Breast Carcinoma and Diet. Analysis of Secondary Statistical Material.** (Ger) Vutuc, C. (Hygiene-Institut, Universitat Wien, Kinderspitalgasse 15, A-1095 Vienna, Austria); Kunze, M. *Wien Med Wochenschr* 128(14): 428-430; 1978.

Possible relationships between breast cancer mortality in women and diet were studied in Austria. In this country, breast cancer mortality has increased by 52% from 1957 to 1974. Concomitantly, the consumption of fat and protein of animal origin has increased by 25.4% and 27%, respectively. These data show a significant positive correlation between increased breast cancer mortality and fat and protein consumption. The findings are in agreement with those observed

in other countries. Among the other factors examined, young age at the first childbirth had no significant influence on breast cancer mortality. (27 refs.)

78-5367 **Nutrition and Carcinoma of the Breast: Preliminary French Investigation.** (Fre) Le, M. (INSERM, Unite de Recherches statistiques, 16 bis, avenue P. Vaillant-Couturier, F 948000 Villejuif, France); Flamant, R. *Bull Cancer (Paris)* 65(1): 65-69; 1978.

A French survey is being conducted to determine if diet is a risk factor in the development of breast cancer in postmenopausal women. A preliminary evaluation of the first 654 questionnaires showed no differences between women with breast cancer and a population of age matched controls with regard to wt, height, or various indices of obesity. (16 refs)

78-5368 **Bilateral Breast Cancer and Familial Aggregations.** (Eng) Sakamoto, G. (Dept. Pathology, Cancer Inst., Tokyo 170, Japan); Sugano, H.; Kasumi, F. *Prev Med* 7(2): 225-229; 1978.

A study was made of the incidence of primary bilateral breast cancer and familial aggregations of this condition among 3,365 Japanese breast cancer patients who underwent mastectomy between 1946 and 1975. The findings were compared with those in Caucasian women. Of the 3,365 patients, 92 had primary bilateral breast cancer; 23 of these cases were simultaneous. The crude incidence of bilateral cancer was 2.7%, compared with 3.0%-6.8% among American women. The true annual incidence rate of breast cancer after surgery for unilateral breast cancer was 3.4/1,000 Japanese patients at risk. Values for American women range from 5.8 to 7.1/1,000. Of the 92 patients with bilateral breast cancer, 13 had a family history of breast cancer among first- to third-degree relatives. In contrast, the familial incidence was only 4.1% among unilateral breast cancer patients. Three of the 13 patients showed multiple familial occurrences, with more than three women being affected within a given family. As many as 46.7% of the bilateral breast cancer patients were nulliparous compared with 18.4% of the unilateral breast cancer patients. Fibrocystic disease was found in association with the cancer in 60% of those in the bilateral group compared with 23% of those in the unilateral group. (8 refs)

78-5369 **Mammographic Patterns and Risk of Breast Cancer.** (Eng) Hainline, S. (Duke Comprehensive Cancer Center, Durham, NC, 27710); Myers, L.; McLelland, R.; Newell, J.; Grufferman, S.; Shingleton, W. *Am J Roentgenol* 130(6): 1157-1158; 1978.

The mammograms 171 women with breast cancer and a and race-matched asymptomatic controls were evaluated check a previous claim that breast cancer risk depends on mammographic classifications N1 (normal breast), P1, (lesser and greater degrees of ductal prominence), and I (dense breast extensively involved with dysplasia). For ea subject, the mammogram of only one breast was examin for all but two of the cancer patients, the mammograms the negative breast were used. The distribution of the f categories among the breast cancer patients was consist with the distribution noted previously. Age-standardized r ratio estimates of the categories, relative to N1, were 1.5 P1, 2.7 for P2, and 7.2 for DY. The cases and controls fered significantly with respect to the distributions of the f categories. It is concluded that ductal prominence and d plasia, as determined by mammography, are significan related to breast cancer risk. (6 refs)

78-5370 **Abnormal Development of the Human Gen Tract following Prenatal Exposure to Dieth stilbestrol.** (Eng) Herbst, A. L. (Dept. Obstetrics Gynecology, Univ. Chicago, Chicago, IL, 60637); Scully, E.; Robboy, S. J.; Welch, W. R.; Cole, P. *In: Incidence Cancer in Humans. Proceedings of the Cold Spring Har Conferences on Cell Proliferation.* Hiatt, H. H.; Watson D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spr Harbor Laboratory): Origins of Human Cancer. Vol. 4, pp.; 399-412; 1977.

Data from the Registry of Clear Cell Adenocarcinoma of Genital Tract in Young Females were used to study dieth stilbestrol (DES)-related abnormalities of the female geni tract. Among 244 registry cases with clear cell carcinon 63% had been exposed prenatally to DES or similar prepa tions and 10% had been exposed to an unknown medicati given because of high-risk pregnancy. Most had been expos before the 18th week of gestation, and the total amount drug taken during pregnancy ranged from 135 to 18,200 m The first case was diagnosed in 1961; the number of ca began to rise strikingly in the late 1960's, and the great number occurred in 1972. There was a sharp rise in t age-specific rate beginning at age 14; it peaked at age 19 a then declined sharply through age 22. The rise in inciden at age 14 suggests that stimuli associated with the onset puberty may be related to the development of many of the tumors. The range of the absolute risk of development adenocarcinoma in a DES-exposed female is 0.14 1.4/1,000. These tumors are considered curable. Nonneopla tic abnormalities commonly found in DES-exposed fema are vaginal adenosis, usually associated with inflammati and squamous metaplasia, and cervical ectropion. These a normalities can be explained by a disturbance in the develo ment of the mullerian epithelium and/or vaginal plate. It likely that endogenous estrogens play a role in the develo ment of tumors in DES-exposed females. (28 refs.)

5371 **Multiple Primary Cancers and Prolonged Survival: Familial Colonic and Endometrial Can-**
s. (Eng) Lynch, H. T. (Creighton Univ. Sch. Medicine, 0 California St., Omaha, NB, 68178); Bardawil, W. A.; rris, R. E.; Lynch, P. M.; Guirgis, H. A.; Lynch, J. F. *Dis lon Rectum* 21(3): 165-168; 1978.

e case histories of a woman and her mother, each of whom eloped multiple primary cancers, and who showed proged survival are presented. The proband was treated at the of 36 for adenocarcinoma of the rectum. Both ovaries and opian tubes were removed at the time of colostomy; in one ıry there was a polypoid nodule that was classified as a all pedunculated fibroma. At age 41, she was treated for ell-differentiated endometrial carcinoma. Her mother had n treated at age 46 for bilateral papillary adenocarcinoma the ovaries and adenocarcinoma of the uterus, at age 59 colonic malignancy, at age 63 for a poorly differentiated cinous adenocarcinoma of the sigmoid colon, at age 67 for enocarcinoma of the transverse colon, at age 70 for a maligncy of the transverse colon, at age 73 for recurrent adenocinoma of the large bowel, and at age 75 for chronic myeenous leukemia. She died at age 79. Analysis of the band's family pedigree indicated that seven persons with ncer (including the proband and her mother) were direct scendants of a maternal grandmother who had died of coic cancer at age 58. Another of the seven had developed ltiple primary tumors of the colon at ages 27 and 48. The ectrum of tumors occurring at an early age among relatives this kindred supports a genetic etiology for the tumors. (13 s)

-5372 **Diet in the Epidemiology of Cancer of the Colon and Rectum.** (Eng) Graham, S. (Dept. Social d Preventive Medicine, State Univ. New York at Buffalo, aulding Quadrangle, Building 2, Room 313, Buffalo, NY, 261); Dayal, H.; Swanson, M.; Mittelman, A.; Wilkinson, *J Natl Cancer Inst* 61(3): 709-714; 1978.

ıe diets of 256 male patients with cancer of colon (CC) and 0 male patients with cancer of the rectum (CR) were exam-ed and compared with those of control patients with nonoplastic, nondigestive diseases. There were 783 controls for e CC patients and 628 controls for the CR patients, and eir age distributions were similar to those of the respective ncer patient group. No increase in risk for CC or CR was served regardless of the amounts of beef or other meats gested. However, an increase in the risk of CC was associat-l with a decrease in the frequency with which vegetables ere eaten. A study of 214 women with CC and 182 women ith CR yielded similar results. The decrease in CC risk asciated with frequent ingestion of vegetables, especially cabge, Brussels sprouts, and broccoli, is consistent with the ecreased numbers of tumors observed in animals challenged ith carcinogens and fed compounds found in these vegetaes. Further studies to determine the effects of the possible contamination of peanut butter by aflatoxins indicated an increased relative risk of CR in men who were currently eating peanut butter, and the risk appeared to increase with years of use. Ingestion of foods salted both during and after cooking was associated with an increased relative risk of colon cancer in men. Several other characteristics of diet were examined, but only slightly suggestive differences were found. (30 refs)

78-5373 **Chronic Anacid Gastritis and Cancer of the Stomach.** (Rus) Druzova, T. A. (Dept. Epidemiology Malignant Tumors, Cancer Res. Center, Moscow, USSR). *Vopr Onkol* 24(7): 103; 1978.

The results of a retrospective study of the role of chronic anacid gastritis in the etiology of stomach cancer are presented. Of 5,000 patients with anacid gastritis, 47 developed stomach cancer. Most (65%) of the tumors were located in the corpus; in contrast, 90% of patients with a history of hyperacid gastritis develop cancer in the antral region of the stomach. (no refs.)

78-5374 **Comparative Study on the Bowel Transit Times in Populations with Different Gastric Cancer Mortalities.** (Jpn) Shimada, A. (Dept. Hygiene, Akita Univ. Sch. Medicine, Akita, Japan); Kamiyama, S. *Jpn J Hyg* 32(6): 712-716; 1978.

Bowel transit times (BTT) and other bowel behaviors were studied at Chokai, Akita Prefecture, and Ohasama, Iwate Prefecture. The male and female gastric cancer mortality of the Chokai inhabitants was 6 and 1.6 times that of the inhabitants of Ohasama, respectively. Transit times of at least 80% excretion of marker pellets were used as an indicator of BTT. BTT of the Akita inhabitants was 34.09 hr, but that of the Iwate inhabitants was 43.89 hr. Frequency of excretion showed the same trend as BTT, with 1.79 (Akita) and 2.20 (Iwate) movements required for excretion of at least 80% of the pellets. About 65% of the stool markers were eliminated at the first movement of the Akita inhabitants, compared with only 50% for the Iwate inhabitants. No differences in frequency of bowel movement were observed between the two regions, but wide individual differences were observed. Stool wt per excretion and stool wt per day were greater for the Akita inhabitants, and these people had a significant correlation between BTT and stool wt. A positive correlation between stool wt per day and 5-day frequency of excretion was noted only in Akita. (7 refs)

78-5375 **Epidemiology of Renal and Ureteral Cancer in Rochester, Minnesota, 1950-1974, with Special**

Reference to Clinical and Pathologic Features. (Eng) Resseguie, L. J. (Dept. Medical Statistics, Mayo Clinic, Rochester, MN); Nobrega, F. T.; Farrow, G. M.; Timmons, J. W.; Worobec, T. G. *Mayo Clin Proc* 53(8): 503-510; 1978.

An analysis was made of the epidemiology of renal and ureteral cancer in Rochester, Minnesota, during 1950-1974 and of the survival of these patients using the thorough medical records available for this population. Ninety cases were identified, 75 renal cell carcinomas (Group 1) and 11 pelvic and 6 ureteral carcinomas (Group 2). For women in Group 1, the incidence of renal carcinoma increased from 1/100,000 in 1950-1954 to 12/100,000 in 1970-1974; no clear trend was seen among men. In Group 1, 27 cases were diagnosed at autopsy (listed as primary cause of death in only 7), and about half of all 73 cases lacked specific symptoms that would focus attention on the urinary tract. Gastrointestinal symptoms were the major complaint in 18/46 cases diagnosed during life. In this group, no patient in whom metastasis was detected at diagnosis survived as long as 5 yr, but patients with carcinoma localized to the kidney cortex (Stage I) had 5- and 10-yr survival rates approx 87% of that expected from the age and sex distribution at diagnosis. Metastases were found in 7/27 cases diagnosed at autopsy and, at last follow-up, in 25/46 cases diagnosed during life. In Group 2, the survival rate was 41% of that expected at 5 yr and 56% at 10 yr. Sixteen patients had symptoms that drew attention directly to the tumor, and all 17 were diagnosed during life. Primary bladder malignancies were found in eight of these patients, but none were found in Group 1. (28 refs.)

78-5376 **The Pattern of Malignant Disease of the Pancreas in Sri Lanka (Meeting Abstract).** (Eng) Attygalle, D. (Faculty Medicine, Sri Lanka Cancer Society, Kynsey R. D. Colombo 8, Sri Lanka). *In: Summary Program and Abstracts of Papers. Proceedings of the 3rd Asian Cancer Conference Held by the Philippine Cancer Society under the Auspices of the Asian Federation of Organizations for Cancer Research and Control in Manila, 26-30 September, 1977.* Philippine Cancer Society. (Manila, Philippines): 184 pp.; 80; 1977. (no refs)

78-5377 **Pleural and Peritoneal Mesotheliomas.** (Ger) Weicksel, P. (Facharzt fur Lungen- und Bronchialheilkunde, Kaiserstrasse 26, D-8700 Wurzburg, W. Germany). *Med Klin* 72(47): 2005-2011; 1977.

A total of 1,687 cases of pleural and peritoneal mesothelioma were registered in different parts of the world during 1963-1976. Of this number, 986 cases were attributed to asbestos exposure, including 744 cases of occupational exposure. (32 refs.)

78-5378 **Lung Cancer Epidemiology (Letter to Edit** (Dan) Wilson, K. (Strandby, Denmark). *Ug* *Laeg* 140(11): 634-636; 1978.

Lung cancer was diagnosed in 15 men who had live Strandby, Denmark, (population approx 1,000) for ≥ yr. All cases were clustered in a small area (population about 500 m from an asphalt factory built 15 yr previou (no refs.)

78-5379 **Morbidity due to Cancer of the Nasal Ca and Maxillary Sinuses in Altai Oblast (US During 1961-1970.** (Rus) Zavarzin, A. A. (Altai Regi Clinical Hosp., Barnaul, USSR). *Zh Ushn Nos Gorl Bo* 1: 51-54; 1978.

The incidence of cancer of the nasal cavity and maxill sinus was studied in Altai Oblast, USSR. From 1961 to 19 there were 164 primary cases of these cancers, which c prised 0.3% of the total cancer morbidity in the district 17.3% of the otorhinolaryngological cancer morbidity. group included 75 men and 89 women. Max morbidity detected among men >50-yr-old and among women 60-yr-old. Of the 125 patients studied histologically, 76 carcinomas, 47 sarcomas, 1 a melanoma, and 1 a p macytoma. Stage I was detected in 9 patients, Stage II in Stage III in 80, and Stage IV in 13. (17 refs)

78-5380 **Nasopharyngeal Carcinoma in Alaskan Nati (Eskimo, Indian, Aleut) 1966-1976 (Meet Abstract).** (Eng) Lanier, A. (Alaska Natives Medical Cen P.O. Box 7-741, Anchorage, AK 99510). *In: Summ Program and Abstracts of Papers. Proceedings of the 3rd As Cancer Conference Held by the Philippine Cancer Society der the Auspices of the Asian Federation of Organizations Cancer Research and Control in Manila, 26-30 Septem 1977.* Philippine Cancer Society. (Manila, Philippines): pp.; 70-71; 1977. (no refs)

78-5381 **Oesophageal Carcinoma in Sri-Lanka--I Deficiency as a Possible Cause of Its High In dence and Its Unusually Common Occurrence in Yo Females (Meeting Abstract).** (Eng) Ganeshananthan, N. Dharmapala Maravite, Ratnapura, Sri-Lanka). *In: Summ Program and Abstracts of Papers. Proceedings of the 3rd As Cancer Conference Held by the Philippine Cancer Society der the Auspices of the Asian Federation of Organizations Cancer Research and Control in Manila, 26-30 Septem 1977.* Philippine Cancer Society. (Manila, Philippines) : pp.; 68-69; 1977. (no refs)

78-5382 **Association of Various Chewing and Smoking Habits with Carcinoma of the Oesophagus (Meeting Abstract).** (Eng) Jafarey, N. A. (Jinnah Postgraduate Medical Center, Karachi, Pakistan); Zaidi, S. H. *In: Third International Symposium on Oncology Held by Taj Pahlavi Cancer Institute in Tehran, 4-8 March, 1978.* Taj Pahlavi Cancer Institute, Pahlavi Medical School, Tehran University. Tehran, Iran): 115 pp.; 105; 1978. (no refs)

78-5383 **The Frequency of Thyroid Gland Carcinoma in Tehran. A Comparison of Surgically Removed Thyroid Gland and Autopsy Findings (Meeting Abstract).** Eng) Bahadori, M. (Dept. Pathology, Tehran Univ., Tehran, ran); Bahadori N. P. *In: Summary Program and Abstracts of Papers. Proceedings of the 3rd Asian Cancer Conference Held by the Philippine Cancer Society under the Auspices of the Asian Federation of Organizations for Cancer Research and Control in Manila, 26-30 September, 1977.* Philippine Cancer Society. (Manila, Philippines): 184 pp.; 88-89; 1977. no refs)

78-5384 **Malignant Neoplasms Following Cardiac Transplantation.** (Eng) Krikorian, J. G. (Div. Oncology, Stanford Univ. Sch. Medicine, Stanford, CA, 94305); Anderson, J. L.; Bieber, C. P.; Penn, I.; Stinson, E. B. *JAMA* 240(7): 639-643; 1978.

Malignant neoplasms developed in 7/124 patients receiving cardiac allografts between January 1968 and April 1977 at Stanford University Medical Center. The mean and median periods of follow-up were 18.3 and 9.7 mo, respectively. There were 3 lymphoproliferative neoplasms, 2 skin cancers, 1 acute leukemia, and 1 colon carcinoma. Of the 35 deaths occurring > 3 mo after transplantation, 4 were due to malignant neoplasms. Comparison of the patients with and without malignant neoplasms showed no significant differences with respect to sex, underlying disease, or blood type. Malignant neoplasms occurred with increased frequency in patients bearing histocompatibility antigens A1, B8, and A1 + B8. The acute myelogenous leukemia may have been due to immunosuppression or therapy with cyclophosphamide. The patients with lymphoproliferative diseases were younger (av age, 20 yr) than the other patients (av age, 50 yr), and their tumors occurred earlier (av time, 33 mo after transplantation) than those in the other patients (av time, 53 mo). The incidence and spectrum of cancers were similar to those observed in recipients of renal homografts. (12 refs)

78-5385 **Mesothelioma in Relation to Asbestos Fibre Exposure: A Review of 70 Serial Cases.** (Eng) Cochrane, J. C. (Natl. Res. Inst. Occupational Diseases, S. African Medical Res. Council, Johannesburg, S. Africa); Webster, I. *S Afr Med J* 54(7): 279-281; 1978.

The relationship of pleural mesothelioma to a history of asbestos exposure was established in 69/70 cases. In one case, it was not possible to elicit a history of significant exposure to asbestos dust. Malignant mesothelioma was confirmed by open thoracotomy biopsy specimens. Detailed environmental and occupational histories were obtained from the patients. Most of the patients were exposed occupationally (asbestos mines, locomotive workshops); the 13 patients with nonoccupational exposure lived on asbestos mine property or in mining areas, where fibers were more or less constantly in the air. The interval from exposure to tumor occurrence ranged from 9 to 40 yr. A minimum of 4 mo of constant exposure to an atmosphere of visible floating asbestos fibers or 4 yr in room contact with loose fibers not visible in the atmosphere was required for adequate and significant exposure. For cases of environmental exposure, a minimum of 3 yr residence in a mining area was required. (9 refs)

78-5386 **Cancer Family Syndrome. A Case Report and Literature Review.** (Eng) Boland, C. R. (US Public Health Service Hosp., 15 and Lake Sts., San Francisco, CA, 94118). *Am J Dig Dis* 23(5, Suppl): 25s-27s; 1978.

A 49-yr-old man, who had survived a right hemicolectomy for adenocarcinoma of the cecum 23 yr earlier, presented with three simultaneous colonic carcinomas in the transverse colon, sigmoid colon, and rectum. Pedigree analysis revealed that he was a member of a family with cancer family syndrome, an autosomal dominant genetic disease in which the affected members are at risk at early age for carcinoma, particularly of the colon and female genital tract. He was a member of a sibship of 13, 5 of whom had had colonic carcinoma at early ages. Endometrial or ovarian carcinoma had been documented in three sisters; one lung cancer and one brain tumor had also occurred among the siblings. Three sibs had solitary adenomatous colonic polyps detected during annual radiographic examinations. The proband's father underwent removal of carcinoma of the cecum at age 27, and he died of carcinoma of the rectum at age 45. The proband's paternal uncle had a colonic carcinoma at age 64, and a paternal aunt died of breast cancer at age 76. The proband's grandfather died of colonic cancer at age 41. No polyps or neoplasms have been documented among the descendants of this sibship. However, in the genetic lines at risk, all members are still under the age of 30. Carcinoembryonic antigen levels in all living members, determined by the Hansen method, were < 4.0 nanograms/ml. (16 refs)

78-5387 **Malignant Melanoma in Spouses.** (Eng) Mintzis, M. J. (Dept. Dermatology, New York Univ.

Sch. Medicine-Bellevue Medical Center, New York, NY); Berger, A. P.; Greenwald, E.; Greenwald, E.; Golomb, F. *Cancer* 42(2): 804-807; 1978.

A study of 743 white patients > 14 yr of age entered in the New York University-Bellevue melanoma registry between 1950 and 1976 revealed three married couples in which both spouses developed malignant melanoma. Statistical calculations based on data supplied by the Third National Cancer Survey and on the 1970 age distribution of married men and women in the US indicated that at most, 0.44 cases of melanoma would be expected to occur among the spouses of the patients. The difference was statistically significant. Various explanations for this occurrence of connubial melanoma are proposed. (1) One explanation is based on the association of melanoma with fair skin and with sun exposure. People tend to marry within their ethnic group, often of a distinctive skin type. All six members of the doubly affected couples had blond hair and blue eyes, features associated with fair skin. (2) Genetic factors or (3) a viral etiology could also be involved. However, the registry records had no information pertaining to any of these issues. (14 refs.)

78-5388 **Actual Volume Doubling Time Values for Pulmonary Metastases from Soft Tissue Sarcomas.** (Eng) Plesnicar, S. (Inst. Oncology, Vrazov trg 4, 61000 Ljubljana, Yugoslavia); Klanjscek, G.; Modic, S. *Cancer Lett* 4(6): 311-316; 1978.

The doubling times of pulmonary metastases in 24 patients with histologically proved soft tissue sarcomas were determined. Among these patients there were 15 cases of fibrosarcoma, 5 of rhabdomyosarcoma, and 1 each of leiomyosarcoma, liposarcoma, hemangiopericytoma, and angiosarco Sixty metastases were measured by chest radiograms on consecutive days, and 116 doubling times were calcula The mean doubling time was 69.9 days. Twenty-two doubl times were eliminated because they were > 100 days lo and the mean for the 941 doubling time values was 37.7 da Metastases with diameters ≤ 14.9 mm had a mean doubl time of 29.7 days; those with diameters of 15.0-111.0 mm h a mean of 43.4 days. Apparently, the slowing of growth rates of these metastases is size dependent. Of doubling times > 100 days, the mean was 207.6 days, w a range of 103.0-370.6 days. When these times were elimi ed, the mean doubling time of the tumors was similar to t previously reported for pulmonary metastases of osteos coma. It is suggested that similar mechanisms govern growth rates of metastases from both types of sarcoma. refs.)

-5389 **Infantile Histiocytosis X (Letterer-Siwe Disease). Investigations with Enzymehistochemical d Sheep-Erythrocyte Rosetting Techniques.** (Eng) Elema, D. (Dept. Pathology, Univ. Groningen, Groningen, Nerlands); Poppema, S. *Cancer* 42(2): 555-565; 1978.

in biopsies and one lymph node specimen from three inits with histiocytosis-X (H-X, Letterer-Siwe disease) were alyzed enzyme histochemically for acid phosphatase (AP), enosine triphosphatase (ATP), leucyl-β-naphthylamidase NA), α-naphthylacetate esterase and peroxidase and by eep erythrocyte rosetting on frozen sections for complent C_3 and for the Fc fragment of IgG. Light microscopy owed a dense dermal and scattered epidermal infiltration histiocytic cells. Electron microscopy showed the ell-known features of H-X cells with often numerous Langhans' cell granules. Most of the cells comprising the specens had weak AP and weak or absent nonspecific esterase tivity but considerable LNA activity. Although its biologil significance is unknown, the uniform presence of LNA ould seem to make it a useful marker for H-X cells. The TP reaction was variable in intensity, ranging from negative strongly positive, and the peroxidase reaction was uniformnegative in the infiltrating cells but was found sporadically the eosinophils. Rosetting techniques indicated the presce of receptors for the Fc fragment of IgG but not r C_3. Cells with the same enzyme histochemical aracteristics could be found in T-cell areas of normal leen, normal and reactive lymph nodes, and thymic edulla but not in B-cell areas or in the thymic core ortex. The enzyme analyses provide additional support r the close relation of H-X cells and Langerhans lls. It is suggested that H-X cells belong to the monouclear phagocyte system and that they are closely nked to the functioning of T-cell-mediated immunity. (44 fs)

8-5390 **Pregnancy and Sarcoma.** (Eng) Jafari, K. (Dept. Obstetrics and Gynecology, Cook County osp., 1825 W. Harrison St., Chicago, IL, 60612); Lash, A. .; Webster, A. *Acta Obstet Gynecol Scand* 57(3): 265-271; 978.

he case reports of six women (aged 15-39) whose pregnanies were complicated by sarcoma are presented. The types nd location of the sarcomas were: pleomorphic sarcoma of ne right leg with pulmonary metastases, osteogenic sarcoma, mphosarcoma, malignant mixed mesodermal tumor of the ulva compatible with sarcoma botryoides, giant cell tumor of the left leg, and liposarcoma of the thigh treated 2 yr previously--metastasis to the lungs appeared during pregnancy. All six women delivered viable infants. The first three women died of their disease within 90 days of delivery, the fourth was lost to follow-up, the fifth is alive with no evidence of disease, and the sixth is in remission. A review of the literature on similar cases is presented. Most authors believe that pregnancy has no deleterious effect on the course of cancer, but this is not supported by adequate data. Fetal or placental metastases are rare. Of 29 reports of maternal cancer metastasizing to the placenta or fetus, 14 were cases of malignant melanoma. (15 refs)

78-5391 **Neoplasia and Dysplasia of the Cervix Uteri and Contraception: A Possible Protective Effect of the Diaphragm.** (Eng) Wright, N. H. (Dept. Community Medicine, Rutgers Medical Sch., Rutgers, NJ); Vessey, M. P.; Kenward, B.; McPherson, K.; Doll, R. *Br J Cancer* 38(2): 273-279; 1978.

The hypothesis that use of a diaphragm is protective against cervical neoplasia (CN) was analyzed in a cohort of women (aged 25-39 yr) entered in a contraceptive study. Among 17,032 women, 65 were found with histologically proved neoplasia or dyplasia diagnosed after cone biopsy prior to September 1, 1977. Two had frankly invasive cancer, 4 microinvasive cancer, 33 carcinoma in situ, 26 dysplasia. The incidence rates of CN in diaphragm users, oral contraceptive users, and intrauterine device users were, respectively, 0.17, 0.95, and 0.87/1,000 woman-yr of observation. The negative relationship between diaphragm use and CN could not be explained in terms of the confounding variables of age, social class, smoking habits, age at first marriage, and age at first pregnancy. It also could not be attributed to a lower frequency of cervical smearing among diaphram users. In more detailed study of 52 of the women with CN and 139 matched controls, information concerning age at first intercourse, numbers of sexual partners, and frequency of cervical smearing outside the clinics was obtained. In comparison with users of other methods of contraception, diaphragm users were less likely to have had coitus at an early age and they had had fewer partners. After adjusting for the effects of these variables, however, the risk of CN was still only about one-quarter that in the users of the other two methods. In this study, smoking emerged as a major risk factor for CN. Smoking habit may reflect some important aspect of sexual behavior relevant to the production of CN that the investigators have been unable to measure. (10 refs)

78-5392 **Effects of Insulin, Human Placental Lactogen and Human Growth Hormone on DNA Synthesis in Organ Cultures of Benign Human Breast Tumours.** (Eng) Welsch, C. W. (Dept. Anatomy, Michigan State Univ., E. Lansing, MI, 48824); Patten, S. E.; McManus, M. J. *Br J Cancer* 38(2): 258-262; 1978.

The effects of bovine insulin (5.0 μg/ml), human placental lactogen (HPL: 10.0 μg/ml), and human growth hormone (HGH: 10.0 μg/ml) on ^{3}H-thymidine incorporation into DNA were studied in organ cultures of 19 benign human breast tumors from 19 premenopausal patients. An attempt was made to determine if HGH has mitogenic activities toward these tumors, as has been reported for HPL. Most of the tumors were classified histologically as fibrocystic disease with varying degrees of adenosis and ductal hyperplasia. There was no correlation between the histopathological diagnosis and response to the hormones. Insulin and HPL significantly ($P < 0.01$) increased the mean incorporation of ^{3}H-thymidine into DNA, but HGH was ineffective. The marked difference in the ability of HPL and HGH to stimulate DNA synthesis in benign human breast tumors, despite their close chemical and physiological properties, may provide insight into the structural entity of HPL required for human mammotrophic activities. The results provide evidence that HPL and insulin, but not HGH, may be important factors in the etiology of benign disease of the human breast. (11 refs)

78-5393 **Migration and Morphological Changes Induced in Normal Cells Treated with Purified Extracts of Conditioned Medium from a Transformed Cell Line (Meeting Abstract).** (Eng) Stocker, M. (Friedrich-Miescher-Institut, P.O. Box 273, CH-4002 Basel, Switzerland); Burk, R. R. *Experientia* 34(7): 958; 1978. (no refs)

78-5394 **Establishment of a Human Plasma Cell Line In Vitro.** (Eng) Burk, K. H. (Dept. Lab. Med., Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030); Drewinko, B.; Trujillo, J. M.; Ahearn, M. J. *Cancer Res* 38(8): 2508-2513; 1978.

The morphological, cytogenetic, ultrastructural, and cell kinetic parameters of a cell line (ARH-77) derived from the peripheral blood of a 33-yr-old woman with IgG plasma cell leukemia were evaluated. The line has been propagated in culture for 2 yr. Morphologically, the ARH-77 cells showed identifiable markers of plasma cells. This was confirmed by electron microscopy, which revealed the presence of substantial (although atypical) endoplasmic reticulum and numerous polyribosomes. An av of 40% cells were positive for IgG by direct immunofluorescence, while IgG-specific radioimmunoassay revealed the production of 1.21 x 10^4 na grams/10^6 plasma cells. The karyotype was aneuploid, w a modal chromosome number of 45-46 and no mark chromosome. Growth kinetic characteristics were: doubl time, 110.4 hr; generation time, 56.4 hr; $G_1 + G_2$-phase tra it time, 45.5; S-phase transit time, 10.9 hr; growth fracti 74%; mitotic index 1.5%; labeling index, 14.3%; and c loss, 31.0%. Some of the growth kinetic characteristics w markedly similar to those displayed in vivo by plasma ce of multiple myeloma patients. The ARH-77 cell line mig be a useful in vitro model for the study of human myelon (15 refs)

78-5395 **Separation of Cells from a Murine Fibrosa coma on the Basis of Size. I. Relationship B tween Cell Size and Age as Modified by Growth In Vivo In Vitro.** (Eng) Grdina, D. J. (Section Experimental Radiot erapy, Univ. Texas System Cancer Center, M. D. Anders Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, T. 77030); Peters, L. J.; Jones, S.; Chan, E. *J Natl Cancer I* 61(1): 209-214; 1978.

Cells from a 3-methylcholanthrene-induced murine fibrosa coma were separated and synchronized on the basis of ce size by centrifugal elutriation. The tumor cells were elutriat immediately after disaggregation of a solid tumor or after hr of incubation in vitro. Cell recovery was > 85%, and ce viability was > 95%. No difference in recovery was observe between cells separated directly from the tumor or followi in vitro incubation. Av cell volume, along with sedimentatio rate, increased with increasing fraction number, indicati that separation was being achieved according to differenc in cell size. The largest size variation was observed amon cells incubated in vitro: modal volumes ranged from 740 2,400 μ^3, and the modal volume of the whole population w 1,620 μ^3. In contrast, cells separated without prior incubatio varied in volume from 60 to 1,400 μ^3, and the modal volum of the population was 980 μ^3. The incubated tumor cells we more readily synchronized than cells separated directly fro the tumor. The reduced synchrony of the latter reflects th heterogeneity of the cell sizes in the same phase of the divisio cycle present in the tumor growing in vivo. In contrast, tumo cells incubated in vitro are exposed to more uniform growt conditions, which minimizes physical differences among th various cell classes and makes the relationship between ce size and age more apparent. (14 refs)

78-5396 **Highly Reiterated Sequences of SIMIAN SIMIANSIMIANSIMIANSIMIAN.** (Eng Rosenberg, H. (Israel Inst. Biological Res., Prime Minister Office, Ness Ziona P.O.B. 19, Israel); Singer, M.; Rosenberg M. *Science* 200(4340): 394-402; 1978.

72-base pair (bp) segment of DNA that is repeated several lion times in the genome of the African green monkey was racterized. The DNA was digested with restriction en- uclease Hind III, and the products were fractionated by trophoresis on polyacrylamide gels. A unique nucleotide uence representing the most abundant residue at each of 172 positions, but not necessarily the structure of any ticular member of the set, is described. The sequence is internally repetitive. The isolated fragments represent a ture of molecules of identical chain length that differ by presence of a nucleotide other than the most abundant at one or more positions. The divergence from the deter- ed sequence within the members of the set is not random. ect quantitation and hybridization kinetics indicate that set occurs several million times within the genome, but reiteration frequency of particular members of the set is known. This uncloned segment was compared with a ned segment of the same DNA that was recombined into genome of a defective, substituted variant of simian virus during permissive infection. The cloned DNA preparation wed no evidence of divergence. The sequences of the ned and uncloned DNA fragments were identical except one position. Thus, the particular DNA may be derived m one of the more infrequent members of the set compris- the monkey fragments. (35 refs)

-5397 **Cell Surface Markers on Pre-leukemic Cells. I. Soluble Proteins.** (Eng) Hollinshead, A. C. ept. Medicine, George Washington Univ. Medical Center, shington, DC, 20037); White, C. S.; Ladoulis, C. T.; Ellis, D.; Gilcher, R. O.; Lessin, L. S. *In: Advances in Compara- e Leukemia Research 1977. Proceedings of the VIIIth Inter- tional Symposium on Comparative Research on Leukemia d Related Diseases, held in Amsterdam, The Netherlands 22-26 August, 1977.* Bentvelzen, P.; Hilgers, J.; Yohn, D. eds. (New York: Elsevier/North Holland Biomedical ess): 503 pp.; 256-259; 1978.

ofiles of soluble membrane proteins from WBC, RBC, and telets of preleukemic patients with hemopoietic dysplasia D) or myeloid metaplasia were compared with those of kemic and normal individuals. Changes in these profiles re examined in relation to those seen during blast crisis and nversion to leukemia. (8 refs)

-5398 **Theoretical Mechanisms for Synthesis of Carcinogen-induced Embryonic Proteins. II. Perbations of Post-translational Nuclear Protein Modifica- n.** (Eng) Hancock, R. L. (High River Inst. Theoretical ncer Study, High River, Alberta, Canada). *Med Hypo- eses* 4(3): 290-301; 1978.

s hypothesized that carcinogenic chemicals initially induce a derepression, typically by an alkylation reaction on specific acidic protein repressors, of structural genes of enzymes that modify the posttranslational structure of nuclear proteins. This causes a cascade of events leading to an array of phenotypic changes. Although massive genic changes in activity may result because of the large number of differentiated cells, only when these changes occur in a stem like cell does the possibility of a neoplastic array of genic expression occur by virture of its repressors being more vulnerable to conformational modification. It is also theorized that there are three major classes of repressors, that may be manipulated via the posttranslational modifying enzymes to become more or less weak, giving rise to a specific differentiated state. It is the repressors synthesized during embryogenesis that are particularly susceptible to derepression. Quasi-differentiated liver stem cells, eg, become relatively easily altered to express many embryonic genes and, if a particular required array of derepression occurs, the overall result would be a large variety of neoplastic clones. However, an organism would have only a limited number of stem cells capable of producing such clones. This would explain the small number of hepatomas produced during chemical induction, although a large number of cells are undoubtedly affected. (39 refs)

78-5399 **Growth Characteristics and Drug Responses of a Murine Lung Carcinoma In Vitro and In Vivo.** (Eng) Kaneko, T. (McEachern Lab., Cancer Res. Unit, Univ. Alberta, Edmonton, Alberta, Canada T6G 2H7); LePage, G. A. *Cancer Res* 38(7): 2084-2090; 1978.

The growth characteristics of a recently established mouse lung tumor line were studied, and several drugs in common clinical use for the treatment of lung cancers were tested in this model system. Nettesheim carcinomas were initially transplanted sc into male DBA/2 mice, and the resulting growths were cultured in vitro. Three cultures slowly developed monolayers of epithelial-like cells that produced tumors when inoculated into DBA/2 mice. The cells were subcultured 15 times, and cloning was carried out with one of the lines. A clone designated KLN205 was selected for further work because it grew relatively rapidly in vitro. This cell line was able to produce lung colonies in male DBA/2 mice when injected into a tail vein, and it could be transplanted sc in male DBA/2 and $BD2F_1$ mice. The sc tumors were composed of poorly differentiated epidermoid carcinoma cells with numerous mitotic figures. The tumors showed evidence of keratinization and frequent extensive areas of necrosis, with a narrow discontinuous zone of lymphocytic infiltration and fibrosis at the periphery. The antimetabolites arabinosyl-6-mercaptopurine and 6-selenoguanosine (SeGR) were used to treat KLN205 cells in vitro. The former was only marginally effective against the lung carcinoma, but the latter was highly effective. 5-Fluorouracil, thioguanine, methotrexate, and adriamycin also had some inhibitory effect in vitro, but methylcyclohexylnitrosourea had no effect. In vivo, only SeGR, thioguanine, and hexamethylmelamine

were significantly effective. This cell line is proposed as a potential model for testing other chemotherapeutic agents. (8 refs)

78-5400 **Proteins Conferred by the Virulence-specifying Plasmid of *Agrobacterium tumefaciens* C-58.** (Eng) Sonoki, S. (Dept. Plant Pathology, Univ. California, Davis, CA, 95616); Kado, C. I. *Proc Natl Acad Sci USA* 75(8): 3796-3800; 1978.

Membrane-associated and periplasmic proteins of *Agrobacterium tumefaciens* C-58 were compared with those from avirulent, nontumorigenic derivative strains by slab and two-dimensional gel electrophoresis. Two proteins (Per-1 a Per-2) with mol wt of 37,500 and 37,000, respectively, we detected in the supernatant fraction of C-58 cells treated wi EDTA and lysozyme. The same proteins were missing fro an avirulent C-58 derivative that did not contain t 117-megadalton plasmid found in the virulent strain. Wh the derivative was mated with C-58, the resulting virule transconjugants regained the large C-58 plasmid and e pressed the Per-1 and Per-2 proteins. When the plasmid w removed from the transconjugants, they became avirule and did not express Per-1 and Per-2. The functional roles these proteins are unknown, but they are associated with t outer membrane and periplasmic fraction of the Agrobacte um cells. The Per-1 and Per-2 proteins appear to be pla mid-coded gene products that may be involved in, but n the sole determinants of, tumorigenesis. (23 refs.)

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CARCINOGENESIS ABSTRACTS

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ABBREVIATIONS

URNAL names are abbreviated according to the *List of Journals Indexed in Index Medicus, Abbreviation ing*. If the journal is not listed in this, abbreviations are derived from the *International List of Periodical Title d Abbreviations*.

NGUAGE of the article is indicated in parentheses after the title and is represented by a three-letter code. source for these codes is *MARC Manuals Used by the Library of Congress*, pages 183-187.

BREVIATIONS used in abstracts:

	angstrom(s)
TH	adrenocorticotropic hormone
P	adenosine diphosphate
P	adenosine monophosphate
P	adenosine triphosphate
rox	approximately
	average
G	bacillus Calmette-Guerin
	twice daily
	degree(s) centigrade
	calorie(s)
al	kilocalorie(s)
	cubic centimeter(s)
	curie(s)
Ci	millicurie(s)
Ci	microcurie(s)
	centimeter(s)
S	central nervous system
	counts per minute
A	deoxyribonucleic acid
50	median effective dose
TA	ethylenediamine tetraacetic acid
	gram(s)
	kilogram(s)
g	milligram(s)
	microgram(s)
	hemoglobin
	hour(s)
	intra-arterial
	intradermal
	Immunoglobulin A
	Immunoglobulin B
	Immunoglobulin G
	Immunoglobulin M
	increased life span
	intramuscular
	intraperitoneal
	International Unit(s)
	intravenous
	Michaelis constant
	lethal dose
50	median lethal dose
	molar
M	micromolar
mOsm	milliosmolar
max	maximum
mEq	milliequivalent(s)
min	minute(s)
ml	milliliter(s)
µl	microliter(s)
mm	millimeter(s)
mo	month(s)
mol wt	molecular weight
N	normal concentration
NAD	nicotinamide adenine dinucleotide
NADH	reduced nicotinamide adenine dinucleotide
NADP	nicotinamide adenine dinucleotidephosphate
NADPH	reduced nicotinamide adenine dinucleotidephosphate
NCI	National Cancer Institute
NIH	National Institutes of Health
PAS	periodic acid-Schiff
po	orally
ppb	parts per billion
ppm	parts per million
qid	four times daily
qod	every other day
QO_2	oxygen quotient
R	roentgen
RBC	red blood cells (erythrocytes)
RNA	ribonucleic acid
rpm	revolutions per minute
sc	subcutaneous
sec	second(s)
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
soln	solution
TCD	tissue culture dose
TCD_{50}	median tissue culture dose
tid	three times daily
UV	ultraviolet
WBC	white blood cells (leukocytes)
wk	week(s)
wt	weight
X	times
yr	year(s)

5401 **Environmental Pathology, Target Environmental Cancer.** (Eng) Garry, V. F. (Dept. Lab. dicine and Pathology, Univ. Minnesota, Minneapolis, N). *Minn Med* 61(5): 328-330; 340; 1978.

tistics show an almost logarithmic increase in overall can- incidence per 100,000 persons over 40 yr of age. Problems screening for environmental carcinogens include the laten- period between exposure and onset of disease, as well as cies differences among experimental animals and man. rrent screening tools are discussed. Occupational bladder ncer and other cancer clusters in Minnesota are reviewed. refs.)

-5402 **Environmental Carcinogenesis.** (Eng) Wynder, E. L. (Dept. Medicine, Memorial Sloan-Ketter- Cancer Center, New York, NY). *Clin Bull* 8(1): 3-9; 1978.

e role of tobacco, alcohol, and diet in cancer induction is scussed, and measures to prevent environmental carcino- nesis are outlined. (46 refs.)

-5403 **Harmful Effect of Water Chlorination with Special Regard to the Cocarcinogenicity of Chlo- e. Part I: Literature Survey.** (Ger) Pfeiffer, E. H. (Hy- ene-Institut, Johannes-Gutenberg-Universitat, D-6500 ainz, W. Germany). *Zentralbl Bakteriol (Orig B)* 166(2/3): 9-184; 1978.

udies of the toxicological aspects of chlorine in water and rtain foods are reviewed. In one experiment, seven genera- ons of BD II rats received tap water containing 100 ppm lorine ad libitum over a 9-yr period. Tumor incidence was e same (approx 10%) as that in controls, which received nchlorinated water. (no refs.)

3-5404 **Nutritional and Environmental Factors in Carcinogenesis (Meeting Abstract).** (Eng) Wynder, . (No affiliation given). *In: Arnold O. Beckman Conference n Biochemistry of Cancer held in San Antonio, September -8, 1978.* American Association for Clinical Chemistry (San ntonio, TX): p. 9; 1978. (3 refs.)

8-5405 **The Environment and Prenatal Origins of Human Disease.** (Eng) Miller, R. W. (Clinical Epidemiology Branch, NCI, Bethesda, MD, 20014). *Excerpta Med Int Congr Ser* (432): 297-302; 1978.

Patterns of discovery of environmental effects on the embryo, monitoring for new human teratogens, teratogenic pollutants (ie, polychlorinated biphenyls, methylmercury), and the interacton of genetics and the environment are surveyed briefly. (23 refs)

78-5406 **Environmental Carcinogens: Mechanisms of Action and Occurrence.** (Ger) Preussmann, R. (Institut fur Toxikologie und Chemotherapie, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, D-6900 Heidelberg 1, W. Germany). *Zentralbl Bakteriol [Orig B]* 166(2/3): 144-158; 1978.

The mechanism of action of known environmental carcinogens is described. These compounds are not carcinogenic per se, but are metabolically bioactivated to electrophilic reactants by chemically reactive intermediates. The electrophilic reactants then form covalent bonds with nucleic acids. This change in the genetic code is in agreement with the mutation hypothesis of carcinogenesis. The bioactivation of aflatoxin B_1 (AFB), N-nitroso compounds, and benzo(a)pyrene (BP) is presented to illustrate this mechanism. Threshold levels (no-effect levels) determined by animal experiments are compared with data on human exposure to BP, AFB, N-nitroso compounds, and vinyl chloride. The difficulties involved in risk evaluations are discussed. (39 refs)

78-5407 **Genetic Variability and Extrapolation from Animals to Man: Some Perspectives on Susceptibility to Chemical Carcinogenesis from Aromatic Amines.** (Eng) Weber, W. W. (Dept. Pharmacology, Univ. Michigan Medical Sch., Ann Arbor, MI, 48109). *Environ Health Perspect* 22: 141-144; 1978.

The predictive value for man of data obtained in other species is illustrated using carcinogenesis arising from exposure to aromatic amines as an example. Studies with an experimental mouse genetics model indicated that the mutagenic effect of acetylaminofluorene (AAF) is related to genetically mediated increases in microsomal oxidative enzyme activity associated with cytochrome P-448. Genetic studies have shown that persons could be classified into two major genetic subgroups, rapid and slow isoniazid acetylators. A genetic polymorphism also exists in rabbits, and the rate of elimination of isoniazid by acetylation is highly correlated in both species

with the amount of isoniazid N-acetyltransferase in the liver. The rate of acetylation of amines with liver homogenates prepared from rapid and slow acetylator rabbits was determined. The results suggest that individuals that are genetically rapid acetylators of isoniazid might also be expected to transform aminofluorene and other hazardous amines to activated carcinogenic forms more rapidly than slow acetylators. The role of this genetic polymorphism as a human determinant of susceptibility to chemical carcinogenesis from aromatic amines is being assessed. (16 refs)

78-5408 **Estimating Cancer Risks to a Population.** (Eng) Schneiderman, M. A. (Field Studies and Statistics Program, DCCP, NCI, Bethesda, MD, 20014); Brown, C. C. *Environ Health Perspect* 22: 115-124; 1978.

General principles guiding current laboratory-to-humans extrapolations of cancer risk are as follows: (1) effects in animals, properly qualified, are applicable to humans; (2) methods to establish a threshold for long-delayed effects of toxic agents such as cancer do not exist; (3) the exposure of experimental animals to toxic agents in high doses is a necessary and valid method of discovering possible carcinogenic hazards in humans; and (4) material should be assessed in terms of human risk, rather than as "safe" or "unsafe". A number of mathematical models have been developed to extrapolate from animal data to human risk of carcinogenesis and to estimate carcinogenic threshold doses. Statistical analysis of standard animal carcinogenicity experiments does not, however, resolve the threshold question, because there are too many biologically reasonable mathematical models, both implying and denying the existence of thresholds, that will fit the observed results. The search for thresholds should not be a search for one specific no-effect dose applicable to all members of the population at risk, but rather a search for many thresholds for each of the population subgroups at various degrees of risk. (20 refs.)

78-5409 **Identification and Reduction of Carcinogens in the Respiratory Environment.** (Eng) Hoffmann, D. (Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY, 10595); Wynder, E. L. *Zentralbl Bakteriol [Orig B]* 166(2/3): 113-135; 1978.

The three major factors responsible for the overall increase in lung cancer (tobacco, air pollution, and industrial chemical exposure) are reviewed. Concerning industrial carcinogenesis, particular attention is focused on bis(chloromethyl)ether, vinyl chloride, benzene, coke oven effluents, asbestos, and nitrosamines. Sources of atmospheric carcinogens and their reduction are outlined. The tumorigenic agents in cigarette smoke are being studied so that a less harmful cigarette can be developed. (58 refs)

78-5410 **Inhalation Carcinogenesis.** (Eng) Nelson, (Inst. Environmental Medicine, New Y Univ. Medical Center, New York, NY, 10016). *Ecotox Environ Safety* 1(3): 289-295; 1977.

A limited review of the carcinogenicity of various inha substances is presented. Chemical hazards in the workp include benzene, nickel carbonyl, mustard gas, vinyl chlor chloroprene, and bis(chloromethyl)ether (BCME). To d at least 35 cases of lung cancer in the US have been attribu to BCME. Several methods for the safe and controlled inh tion of experimental animals to carcinogenic material are lined. (22 refs)

78-5411 **Carcinogenesis and Aging.** (Eng) Magee, P. (Fels Res. Inst., Temple Univ. Sch. Medic Philadelphia, PA, 19140). *Adv Exp Med Biol* 97: 133- 1978.

Factors affecting carcinogenesis that might be influenced age are reviewed. Evidence that some human cancer is cau by chemicals is derived from studies on occupational other forms of exposure and from studies on the geograph pathology of cancer. Studies with migrant populations i cate that genetic factors do not play a major role in the g graphical variations of some cancers and that these variati are the result of environmental factors. Since the efficac most chemical carcinogens is dependent on the balance tween their metabolic activation and deactivation, char in the activities of any of the enzyme systems involved co influence their carcinogenic effects. Some enzyme activi are known to vary with age, but it is too early to draw con sions on the effects of these changes on tumor induct DNA appears to be the most likely target for the activa forms of chemical carcinogens, but there is no evidence any decline in DNA repair with increasing age. Cancers t are influenced by hormonal balance, including mammary prostatic cancer, may be affected by age-related change the endocrine system. There is substantial evidence from man and animal studies that the increasing incidence of c cer with increasing age simply reflects the longer time t the cells have been exposed to carcinogens. (53 refs)

78-5412 **Can Permissible Levels of Carcinogenic C pounds in the Environment Be Envisaged? C cal Remarks.** (Eng) Truhaut, R. (Centre de Recherches T icologiques, Faculte des Sciences Pharmaceutiques Biologiques, Universite Rene Descartes, 75006 Pa France). *Ecotoxicol Environ Safety* 1(1): 31-37; 19

Arguments for and against the theory of no thresholds carcinogens are reviewed. The data available on dose/ef relationships for most environmental carcinogens, especi at low levels, are limited. Since all chemical carcinogens p

hazard, human exposure must be reduced to a socially acptable level, similar to the approach taken with ionizing diation. Such an approach will avoid the imposition of a rdship or of an unrealistic economic burden. (13 refs)

8-5413 **Methods of Analyzing Environmental N-Nitrosamines.** (Rus) Kostiukovskii, I. L. (Inst. Nuition, Moscow, USSR); Melamed, D. B. *Gig Sanit* (1): 3-68; 1978.

Methods of identifying, purifying, and determining environental N-nitrosamines (NA) are reviewed. The following rotocol is recommended for isolating and purifying IA: homogenization, stem distillation, distillation, evaporaon from an acid and then alkaline medium, extraction, risg and dehydration of the extract, and chromatographic urification. Gas-liquid chromatography with nitrogen-sensive detectors, chromatography/mass spectrometry, chemiluinescence, and Raman spectroscopy can be used to detect ese compounds. (51 refs)

8-5414 **An Assessment of Human Exposure to N-Nitroso Compounds.** (Eng) Fine, D. H. (Thermo Electron Res. Center, Waltham, MA). *IARC Sci Publ* (19): 67-278; 1978.

Current knowledge concerning nitrosamine (NA) impurities s reviewed, and data on known exposure routes are normalzed to their relative significance in terms of NA exposure er person per day. Volatile NA's are ingested in nirite-preserved foods; data are not available for the occurence of nonvolatile NA's in foods. N-Nitrosodimethylamine s present in wastewater from chemical factories at levels of 0.2-5 μg/liter, but the < 0.01-μg/liter levels of NA'a found n drinking water are considered insignificant. Airborne NA's re inhaled in localized areas around certain specialized industries, tobacco smoke, aqueous mists of herbicides, and cutting fluid vapors. Dermal contact is experienced by machinists who handle machine parts that are wet with cutting luid, agricultural workers who formulate or apply herbicides, and by persons (especially actresses and models) who se facial cosmetics, hair shampoos, hand lotions, and skin creams. All of these substances contain significant amounts of NA's. Tumors have been induced in laboratory animals by po administration of precursor amines + nitrite, presumably via in vivo nitrosation. In vivo nitrosation also takes place in humans fed diphenylamine + nitrite. Possible N-nitrosation mechanisms are presented. A high pH does not necessarily minimize the reaction, and in vivo nitrosation proceeds at a rate considerably faster than the one that could be predicted by conventional kinetics. (37 refs)

78-5415 **Interference of Carcinogens with Information Structures.** (Ita) Prodi, G. (Istituto di Cancerologia, Universita, Bologna, Italy); Grilli, S. *Recent Prog Med (Roma)* 63(6): 549-570; 1977.

The molecular mechanisms of chemical and viral carcinogenesis and relationships between mutagenesis and carcinogenesis are reviewed. The mechanisms of action of polycyclic aromatic hydrocarbons, aromatic amines, and nitrosamines are described. (37 refs)

78-5416 **Determinatioon of N-Nitroso Compounds by Mass Spectrometry. A Review.** (Eng) Gough, T. A. (Lab. Government Chemist, Cornwall House, Stamford St., London SE1 9NQ, England). *Analyst* 103(1229): 785-806; 1978.

The detection of N-nitroso compounds, particularly the volatile N-nitrosamines, by mass spectrometry and by gas chromatography-mass spectrometry is reviewed, and the merits of these and other procedures reported in the literature are assessed. N-nitrosamines have been found in food, polluted air, industrial and agricultural chemicals, tobacco products, and drugs. (200 refs)

78-5417 **Experiments With In-Vitro-Test Systems to Prove Mutagenic Substances.** (Ger) Greim, H. (Munich, W. Germany); Goggelmann, W.; Wolff, T. *Staub-Reinhalt Luft* 38(6): 227-232; 1978.

Some relatively simple in vitro tests use bacteria or mammalian cells to identify mutagenic chemicals; the test compounds are metabolically activated by liver microsomes or the S-9 fraction with corresponding cofactors. The most widely used bacteria test systems, the Ames test and the Liquid test, are discussed with emphasis on problems that complicate the interpretation of test results, including those related to a compound's metabolism. Methods used to identify chemical mutagens in mammalian cells are summarized. (37 refs)

78-5418 **Experimental Carcinogenesis and Mutagenesis.** (Fre) Chouroulinkov, I. (Institut de Recherches Scientifiques sur le Cancer, BP-8, 94800 Villejuif, France). *Ann Mines* 184(7/8): 51-56; 1978.

The general hypotheses of carcinogenesis (genetic and epigenetic theories, viral gene activation, and cellular selection) are reviewed with special regard to the hypothesis on somatic mutations and the relationship between the carcinogenic and mutagenic properties of chemicals. A review of the literature shows that 88% of the tested carcinogens were also found to be mutagens, and 24% of the noncarcinogens were mutagens. Inversely, 93% of the mutagens and 61% of the nonmutagens proved to be carcinogens. (45 refs)

78-5419 **Aspects of Carcinogenesis.** (Ger) Reusch, K. (Institut fur Toxikologie und Chemotherapie, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, 6900 Heidelberg, W. Germany). *Roentgenpraxis* 31(9): 197-204; 1978.

The mechanisms of chemical carcinogenesis are reviewed. The metabolic activation of a substance to a reactive product (ultimate carcinogen), the interaction of this product with cellular macromolecules, and the induction of changes in the genetic information of the cell are the principal events in chemical carcinogenesis. (11 refs)

78-5420 **Bladder Carcinoma after Long-Term Treatment with Cyclophosphamide for Multiple Myeloma.** (Ger) Schmidt, C. G. (Innere Klinik und Poliklinik, Westdeutsches Tumorzentrum, Universitat Essen, Hufelandstrasse 55, D-4300 Essen 1, W. Germany). *Urologe[A]* 17(2): 109-110; 1978.

A patient with multiple myeloma developed carcinoma of the urinary bladder after long-term treatment with cyclophosphamide (total dose 135 g po). Most tumors that occurred after cytostatic therapy were found in patients treated with cyclophosphamide. This drug should not be used in the treatment of nonneoplastic diseases. (no refs)

78-5421 **A Review of the Genetic Toxicology of Chlorinated Dibenzo-p-dioxins.** (Eng) Wassom, J. S. (Environmental Mutagen Information Center, Information Center Complex/Information Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830); Huff, J. E.; Loprieno, N. *Mutat Res* 47(3/4): 141-160; 1978.

Published and unpublished information on the genetic toxicology of chlorinated dibenzo-p-dioxins, particularly 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), is reviewed. TCDD may be formed along with other dioxin compounds during manufacture of the herbicide 2,4,5-trichlorophenoxyacetic acid, the fungicide pentachlorophenol, and the germicide hexachlorophene. Research on dioxins as potential mutagens was initiated because of their structural similarity to acridines, a class of known intercalating agents. Only four dioxins have been evaluated for mutagenicity: the di-, tetra-, and octachlorinated derivatives and the unsubstituted dibenzo-p-dioxin. The results of these evaluations are inconclusive. Experiments with mice suggest that TCDD may be a hepatocarcinogen because of its specific cytological effect on proliferating hepatocytes. However, the cytological effects produced by TCDD in the liver of animals may be due to the toxic effects of the short-term high dose levels administered and to the fact that TCDD tends to concentrate in the liver. The positive mutagenic and cytological effects reported with few dioxin isomers examined seem to depend on the posit of chlorine substitution, with TCDD being the most act form. Preliminary results of cytogenetic analyses of mater blood and abortive fetal tissue from persons exposed TCDD in Seveso, Italy (accidental release from a chemi plant), are inconclusive. However, workers exposed to herbicides Klorinol and Buvinol, which may have vary levels of TCDD contamination, had a higher incidence chromatid breaks in peripheral lymphocytes than non posed individuals. The conflicting results of mutagenic tests with dioxins could be due to solubility problems, tre ment protocols, sample purity, and the extremes in toxic of these compounds. (70 refs)

78-5422 **Genetic Toxicology of Lysergic Acid Diethy mide (LSD-25).** (Eng) Cohen, M. M. (Dept. H man Genetics, Hadassah-Hebrew Univ. Medical Cen Jerusalem, Israel); Shiloh, Y. *Mutat Res* 47(3/4): 183-2 1978.

The clastogenicity, mutagenicity, teratogenicity, and cogenicity of the hallucinogen lysergic acid diethylam (LSD-25) are reviewed. It is impossible to draw clear-cut c clusions regarding any of the biological effects of LSD, spite of the considerable scientific effort invested. Much the difficulty arises from the lack of similarity of the perimentation and, therefore, the lack of comparability. M in vitro studies of the clastogenicity of LSD indicate t there is either a suppression of mitosis or enhanced chron some damage. However, extrapolation of these results to in vivo situation is difficult. In humans, no consensus can made with respect to chromosome breakage, and the inc sistencies within and between studies remain inexplicab However, several controlled investigations of the in vivo fect of chemically pure LSD suggest that it produces a tr sient increase in lymphocyte chromosome breakage. In c trast, the results of cytogenetic studies in animals contradictory. Although human mutagenicity studies nonexistent, in those experimental organisms tested, usi accepted techniques, LSD proved to be at best a weak mu gen. Teratogenicity studies in animals are confusing becau of the large number of animal species and strains, dosag and parameters studied. With regard to humans, howev enough time has elapsed after exposure for any such effe if it exists, to have been expressed, and it can be conclud that LSD is not teratogenic in humans. As to the drug's onc genic potential, the three reported cases of leukemia in LS users are probably the result of coincidence. (160 refs)

78-5423 **Epidemiological Studies of the Occupatio Hazards of Anaesthesia--A Review.** (Eng) V

M. P. (Univ. Dept. Social and Community Medicine, eble Road, Oxford OX1 3QN, England). *Anaesthesia*): 430-438; 1978.

British, and Scandinavian studies of the possible occupaal hazards of anesthesia were reviewed. The studies, pubed in the period 1968-1977, indicate a moderate increase he risk of spontaneous abortion among exposed women. re is no convincing evidence of any other hazards such alformation of offspring, stillbirth, low birth wt, or infer-. (14 refs)

5424 **About Comparative Sensitivity of Certain Methods of "Drugs" Mutagenicity Estimation eeting Abstract).** (Eng) Revazova, J. (Res. Inst. Biological ting Chemicals, Moscow Region, USSR); Radchenko, L.; tslavsky, V.; Podolnaya, M. *Mutat Res* 53(2): 252; 1978. refs)

5425 **Mutagenicity of Hair Dyes: Some More Evidence and the Problems of its Interpretation eeting Abstract).** (Eng) Venitt, S. (Div. Chemical Carcinoesis, Inst. Cancer Res., Pollards Wood Res. Station, htingales Lane, Chalfont St. Giles, Bucks, England). *tat Res* 53(2): 278-279; 1978. (no refs)

5426 **Review of Submammalian Systems for Detecting Mutagens and Carcinogens (Meeting Abact).** (Eng) Sugimura, T. (Natl. Cancer Center Res. Inst., kyo, Japan). *Mutat Res* 53(2): 270-271; 1978. (no refs)

-5427 **Deficiencies in the Microbial Activation System for Mutagenic-Carcinogenic Screening (Meet Abstract).** (Eng) Rinkus, S. (Div. Environmental Toxology and Epidemiology, Univ. Texas Medical Branch, lveston, TX, 77550); Legator, M. *Mutat Res* 53(2): 254; 78. (no refs)

-5428 **In Vivo Cytogenetic Screening of Drugs for Mutagenic Potential (Meeting Abstract).** (Eng) uchimoto, T. (Biological and Medical Res. Div., Sandoz Ltd., Basel, Switzerland); Matter, B. E. *Mutat Res* 53(2): 277; 1978. (no refs)

78-5429 **Metal Carcinogenesis (Meeting Abstract).** (Eng) Sunderman, F. W. (No affiliation given). *In: Arnold O. Beckman Conference on Biochemistry of Cancer held in San Antonio, September 6-8, 1978.* American Association for Clinical Chemistry (San Antonio, TX): p. 9; 1978. (3 refs)

78-5430 **Pseudolymphomas and Lymphomas Induced by Hydantoins.** (Fre) Reiffers, J. (Service d'Hematologie, Hopital Henri-Mondor, Bordeaux, France). *Nouv Rev Fr Hematol Blood Cells* 20(1): 131-137; 1978.

Literature cases of patients who developed pseudolymphomas (PL) and malignant lymphomas after treatment with phenytoin or diphenylhydantoin are reviewed. More than 90 patients with PL and 19 with lymphomas have been reported. The similarity of the PL induced by hydantoins to immunoblastic lymphadenopathy and the precancerous nature of PL are discussed. (52 refs)

78-5431 **Hepatic Changes Produced by Contraceptive Steroids.** (Spa) Uribe, M. (Departamento de Gastroenterologia, Instituto Nacional de la Nutricion, San Fernando y Viaducto Tlalpan, Mexico City 22, Mexico); Ramos de Uribe, M. H.; Cario, A. A. *Rev Gastroenterol Mex* 42(3): 139-147; 1978.

The side effects of hormonal contraceptives include jaundice, cholestasis, hepatitis, hepatic adenoma, and liver cancer. Literature cases of hepatic adenoma and liver carcinoma number about 250 and 21 patients, respectively. (75 refs)

78-5432 **Estrogens and Risk of Carcinoma. Practical Consequences for Estrogen Therapy.** (Ger) Kaiser, R. (Univ.-Frauenklinik, Kerpener Strasse 34, D-5000 Cologne 41, W. Germany). *Munch Med Wochenschr* 120(37): 1185-1186; 1978.

Relationships between estrogen treatment and cancer in women are discussed. An association between estrogen treatment and precancerosis or carcinoma of the endometrium cannot be ruled out with certainty. There is no firmly established relationship between breast cancer and estrogens. (no refs)

78-5433 **Genetic Effects of Coumarins.** (Eng) Grigg, G. W. (Molecular and Cellular Biology Unit, CSIRO, P.O. Box 184, North Ryde 2113, New South Wales, Australia). *Mutat Res* 47(3/4): 161-181; 1978.

Coumarins (CM) that modify or cause the cell to modify the structure or properties of genetic material, except for the brightening agents (psoralens, or furocoumarins) and the aflatoxins, which have been surveyed recently, are reviewed. CM have been shown to induce C-mitotic effects, chromosome breakage, and various sorts of rearrangements and to affect DNA repair and mutation frequency in bacterial, plant, and animal cells. The hepatic toxicity to rats that showed up in routine toxicology tests caused the voluntary withdrawal of CM from the foodstuffs industry, in which it was used as a flavoring substance. Tests with rats and dogs indicated that feeding CM initiated liver damage by damaging the endoplasmic reticulum. The principal metabolite of CM in rats, O-hydroxyphenylacetic acid, is thought to be the main cause of liver toxicity to the animal. The emergence of lines of rodents resistant to the CM derivative coumadin (warfarin) indicates that there is a genetic variability in the toxic response to the drug or in its metabolism in these animals. A similar variability emerged in human studies. Patients have been reported as being very sensitive or resistant to the anticoagulant dicoumarol. Many CM are effective chromosome-breaking agents, yet others have antimutagenic activity (coumadin). In one study high levels of CM (0.5% of diet for 2 yr) were hepatocarcinogenic in rats, but in another CM suppressed 7,12-dimethylbenzanthracene-induced breast carcinomas in rats, possibly because of its ability to modify the activity of liver microsomal enzymes. Long-term adjuvant therapy with coumadin, phenprocoumon, and discoumarol enhanced the survival of cancer patients. Experiments with mice indicated that CM enhances survival by preventing metastasis. The paradoxical effects of CM are similar to those of caffeine, which has been found to be a chromosome-breaking agent, a mutagen, and an antimutagen. The fact that both caffeine and CM bind selectively to single-stranded DNA and consequently destabilize the double helical conformation in favor of the random coil configuration may help to explain their genetic properties. (152 refs)

78-5434 **PUVA: A Caution.** (Eng) Segal, S. (No affiliation given); Cohen, S. N.; Freeman, J.; Hill, R. M.; Kagan, B. M.; Kauffman, R. E.; Pruitt, A. W.; Soyka, L. F.; Vickers, S. M. *Pediatrics* 62(2): 253; 1978.

Caution should be exercised in the use of a form of photochemotherapy known as PUVA (psoralen with UV light in the A range) for the treatment of severe psoriasis. PUVA produces changes in DNA that have been linked experimentally to teratogenesis and carcinogenesis. Under no circumstances should children be treated with PUVA, except under established IND (investigational new drug) protocols. (7 refs)

78-5435 **Toxic Effects of Vinyl Chloride.** (Ger) Veltr G. (Univ.-Hautklinik Bonn-Venusberg, D-5 Bonn 1, W. Germany); Lange, C. E.; Stein, G. *Hau* 29(4): 177-182; 1978.

The toxicological aspects of vinyl chloride (VC) are revie on the basis of examinations of workers occupationally posed to VC over long periods of time. The liver histo revealed periportal, septal, and intralobular fibrosis; focal reticular collagenization of the sinusoid walls; hepatocyt generation; and activation and proliferation of the sinu cells, with cell atypia and transition into angiosarcoma oc ring in some cases. The metaphase analysis revealed nc markable pathological changes; ie, no mutagenic effect of (35 refs)

78-5436 **Vinyl Chloride and Vinyl Benzene (Styre Metabolism, Mutagenicity and Carcinoge ty.** (Eng) Vainio, H. (Dept. Industrial and Toxicology, Occupational Health, Haartmaninkatu 1, SF-00290 Hels 29, Finland). *Chem Biol Interact* 22(1): 117-124; 1978.

The metabolism, mutagenicity, and carcinogenicity of v chloride, (VC) and vinyl benzene (styrene) are reviewed b ly. VC and styrene are mutagenic in bacterial test syst Drosophila, yeast, and mammalian cells. The mutageni of VC in bacterial test systems depends, at least partially metabolic activation by microsomal enzymes. Chloroe lene oxide, the primary biotransformation product of VC a potent mutagenic and alkylating agent. Styrene is muta ic to *Salmonella typhimurium*, but only after metabolic a vation, whereas styrene oxide, its primary biotransforma product, is mutagenic to *Salmonella* without activation several studies, an excess of chromosome aberrations (c pared with controls) was found in the lymphocytes of wo ers exposed to VC monomer. In addition, an excess fetal occurred among women whose husbands are heavily expo to VC. Workers exposed to styrene also had increa chromosome aberrations in their lymphocytes. Both chl ethylene oxide and styrene oxide bind covalently to cell macromolecules. VC is carcinogenic in rats (skin, lung, bo liver) and humans (liver, brain, lung, and lymphatic tiss Styrene oxide was a weak carcinogen when applied to mo skin. Styrene is currently being tested in animals. These fi ings raise concern about the possible genetic risks of VC styrene to humans. (55 refs)

78-5437 **How Much Benzene Causes Cancer?** (E Thorpe, J. J. (Exxon Corp., New York, N *Hydrocarbon Process* 57(5): 172-174; 1978.

Data on the acute and chronic toxicity and carcinogeni

enzene are reviewed. Although benzene has not induced emia in experimental animals, it appears that occupation- xposure to benzene is causally related to acute myeloge- s leukemia and its variants. Arguments for and against new US permanent standard (February 1978) are present- (10 refs)

5438 **Antigens of Chemically Induced Sarcomas: Their Possible Origins and Interrelationships.** g) Blackstock, R. (Dept. Pediatrics, Univ. Oklahoma alth Sciences Center, Oklahoma City, OK, 73100). *South d J* 71(5): 586-590; 1978.

tigens on the surface of chemically induced tumors (ACT) categorized, and their relationship to H-2 antigens is dis- sed. There are four types of ACT: tumor-specific antigens, al or embryonic antigens, viral antigens, and normal tissue igens. ACT have several characteristics in common with rmal H-2 alloantigens of mice: both serve as targets for nsplantation immunity, both have similar cell-surface lo- ion and mobility, and both show a high degree of polymor- ism. (104 refs)

-5439 **Immunoproliferation and Cancer: A Common Macrophage-derived Promotor Substance.** ng) Salmon, S. E. (Section Hematology and Oncology, niv. Arizona Coll. Medicine, Tucson, AR, 85724); Ham- rger, A. W. *Lancet* 1(8077): 1289-1290; 1978.

is hypothesized that a common proliferative factor is re- ired for the growth of clones of both antigen-triggered B mphocytes and carcinogen-triggered epithelial cells and at this factor is secreted by macrophages that have original- differentiated in support of the immune response. The pro- oter in the two-stage model of carcinogenesis in mouse skin duces epithelial proliferation and intense cutaneous infiltra- on with inflammatory cells. Viable adherent splenic macro- ages from mineral oil-treated BALB/c mice produce a fac- r that, in concert with 2-mercaptoethanol (2-ME), romotes soft-agar coloney formation by human myeloma lls. Medium conditioned by the oil-primed BALB/c macro- ages is able to support in vitro tumor colony growth from esh biopsy specimens of a wide variety of cancers. Normal urine B-lymphocyte colony formation also requires 2-ME nd is promoted by a soluble factor elaborated by macro- ages. Thus, both immune and tumor clones may require common and specific growth stimulus that promotes clonal roliferation of an already triggered hypermutable cell popu- tion. This factor would also incidentally stimulate the rowth of clones of tumor cells that had been previously on- ogenically transformed. Some clinical features of metastasis may also be consistent with the role of the macrophage as a promoter of tumor growth. (15 refs)

78-5440 **Hamster Immune Responses: Experimental Models Linking Immunogenetics, Oncogenesis and Viral Immunity. Introduction.** (Eng) Streilein, J. W. (Dept. Cell Biology, Univ. Texas Health Science Center, Dallas, TX, 75235). *Fed Proc* 37(7): 2023-2024; 1978.

Subjects covered at a symposium on hamster immune responses are outlined. The topics include the normal immune response, immunogenetics and transplantation, response to infection (particularly viral), and tumor immunity, along with the high susceptibility of hamsters to oncogenic agents, their low spontaneous rate of malignant degeneration, and the development of spontaneous lymphomas in a hamster colony. (no refs)

78-5441 **Epstein-Barr Virus as the Cause of a Human Cancer.** (Eng) Epstein, M. A. (Dept. Pathology, Univ. Bristol, Bristol, England). *Nature* 274(5673): 740; 1978.

Although Epstein-Barr virus (EBV) appears to be the cause of Burkitt's lymphoma, a climate-dependent cofactor, possibly malaria, also appears to be involved in the disease. The fact that only B cells have receptors for EBV and that malaria is both immunosuppressive and a stimulator of B-cell proliferation support this idea. The malaria may stimulate and maintain a subclass of B cells susceptible to EBV-induced transformation. (20 refs.)

78-5442 **Biological Approaches to Human Cancer Virus Detection.** (Eng) Kaplan, H. S. (Cancer Biology Res. Lab., Dept. Radiology, Stanford Univ. Sch. Medicine, Stanford, CA, 94305). *Prog Exp Tumor Res* 21: 2-18; 1978.

Procedures for detecting a human cancer virus are outlined in detail. The first step is the cultivation of freshly procured human tumor tissue in vitro. Care must be taken to insure that the culture is not infected with other cell lines. Cultured cells should be identified by morphological, cytochemical, and surface marker techniques with the original population, and it must be shown that they have the biological characteristics of neoplastic cells. The cultures should then be examined for release of viruses and the presence of viral antigens and reverse transcriptase. Cocultivation of the tumor cells with indicator cell lines derived from the same and other species is a sensitive technique for the transcellular transmission and detection of candidate viruses. Since the expression

of virus-specific antigens and the replication of infectious virus may be under strict control of the host genome, the cultures should be subjected to treatment that interferes with the host cell gene regulatory mechanisms. Once virus particles are isolated, they should be tested for oncogenicity in subhuman primates and congenitally athymic nude mice. Also, normal human cells infected with the virus could be propagated in vitro and observed for distinctive changes. Another approach would be to inject the putative tumor virus into rabbits or goats, isolate tumor antiserum, and test the antiserum for specificity against the original tumor. If positive reactions are observed with virus-specific antigens, the serum could be used to screen other tumors of the same morphology from other patients. A candidate human tumor virus that is truly the cause of the tumor from which it was isolated should induce the same or similar antigens in all similar-type tumors. (77 refs)

78-5443 **The Immunological Approach to Study of Possibly Virus-induced Human Malignancies Using the Epstein-Barr Virus as Example.** (Eng) Henle, W. (Div. Virology, Joseph Stokes, Jr. Res. Inst., Children's Hosp. Philadelphia, Conshohocken Ave., Philadelphia, PA, 19131); Henle, G. *Prog Exp Tumor Res* 21: 19-48; 1978.

Immunological evidence linking Epstein-Barr virus (EBV) with Burkitt's lymphoma (BL) and nasopharyngeal carcinoma (NPC) by serologic surveys and by detection of EBV-determined antigens in tumor cells is reviewed. Particular attention is focused on antibody titers to the various EBV antigens in BL and NPC. The role of EBV in infectious mononucleosis is also reviewed. Since BL and NPC have either immunosuppressive effects or require therapy by immunosuppressive agents, activation of the latent persistent viral carrier state in patients with high anti-EB viral capsid antigen titers appears to be the most plausible explanation for the elevated antibody titers. (121 refs)

78-5444 **On the Toxicity of Inhaled Hot Particles with Special Reference to Plutonium.** (Eng) Muth, H. (Institut fur Biophysik, Universitat des Saarlandes, Boris Rajewsky-Institut, D-6650 Hamburg, W. Germany); Jacobi, W.; Feinendegen, L. E.; Hug, O.; Oberhausen, E. *Radiat Environ Biophys* 15(1): 1-11; 1978.

A review of the epidemiological literature indicated that after >30 yr of work with ^{239}Pu in the US, no lung cancer cases could be attributed to the incorporation of Pu. Experimental studies in animals gave no indication that hot-particle inhalation leads to a larger risk of lung cancer than homogeneous irradiation. It is suggested that no reduction in the existing limit for inhalation of insoluble ^{239}Pu compounds be ma (35 refs)

78-5445 **Asbestos Fibre Dust and Gastro-intesti Malignancies. Review of Literature with gard to a Cause/Effect Relationship.** (Eng) Miller, A. (NCIC Epidemiology Unit, Univ. Toronto, 121 Saint Jos St., Toronto, Ontario, M5S 2R9, Canada). *J Chronic* 31(1): 23-33; 1978.

A review of the literature on the association between ex sure to asbestos dust and gastrointestinal malignancies dicated that such an association does exist, particularly cancer of the esophagus, stomach, colon, and rectum. In absence of an explanation to the contrary, this exposure m be regarded as causal. There appears to be a latent period $\geq$20 yr between the first exposure and the development malignancy. A worker with $\geq$20 yr asbestos exposure approx a threefold greater risk of gastrointestinal cancer th an unexposed individual. There is no evidence that other f tors contribute to or subtract from this association. (39 re

78-5446 **Assessment of Hazards in Engineering Wo** (Eng) Kinchin, G. H. (Safety and Reliabi UKAEA, Culcheth, Warrington, England). *Proc Institu Civil Eng* 64: 431-438; 1978.

Acceptable risk criteria to be incorporated in the design nuclear power plant facilities are outlined. (14 refs)

78-5447 **Low-Dose Radiation: The Hanford Evide (Letter to Editor).** (Eng) Stewart, A. (Regio Cancer Registry, Queen Elizabeth Hosp., Birmingham 2TH, England). *Lancet* 1(8072): 1048-1049; 1978.

Data on deaths and radiation doses at a plutonium plant th was monitored from 1944 to 1972 suggest that the cancer r from the current permissible dose (5 rads/yr) could be as hi as 1/150. The mean dose was higher for the 760 employ with fatal cancers than for the 2,850 employees with dea due to other causes. Expansion of nuclear facilities should curtailed until correct measures of the cancer hazard made. (4 refs)

78-5448 **Derepression of a Dormant Bacteriophage a Test for Potential Carcinogens (Meeting A stract).** (Eng) Devoret, R. (Section de Radiobiologie C

re, Laboratoire d'Enzymologie, CNRS, 91190 sur-Yvette, France); Moreau, P.; Bailone, A. *Mutat Res*): 178-179; 1978. (4 refs)

5449 **Experience and Correlation of Bacterial Mutagenic Tests (Meeting Abstract).** (Eng) Watkins, A. (Pharmaceuticals Div., Imperial Chemical Industries , Macclesfield, Cheshire, England). *Mutat Res* 53(2): 283; 3. (no refs)

5450 **Fundamental Mutagenic Mechanisms (Meeting Abstract).** (Eng) Drake, J. W. (Dept. Microbiy, Univ. Illinois, Urbana, IL, 61801). *Mutat Res* 53(2): -181; 1978. (no refs)

5451 **Human Inherited Disease with Altered Mechanisms for DNA Repair and Mutagenesis.** (Eng) aver, J. E. (Lab. Radiobiology, Univ. California, San ncisco, CA). *Excerpta Med Int Congr Ser* (432): 85-100; 8.

ariety of human disease (ie, xeroderma pigmentosum and xia telangiectasia) involving increased cancer risk and asiated disorders in the CNS, in hematopoietic, immunolog, ocular, and cutaneous tissues, and in embryological deopment have defects in biochemical pathways for excision air of damaged DNA. Excision repair has multiple nches by which damaged nucleotides, bases, and ss-links are excised, and it required cofactors that control access of repair enzymes to damage in chromatin DNA. refs)

-5452 **Growth Factors for Tumours.** (Eng) Shields, R. (Imperial Cancer Res. Fund Lab., London, End). *Nature* 272(5655): 670-671; 1978.

idence that ectopic growth factors are involved in tumor owth and development is summarized. A human fibrosarma cell line produces a growth factor similar to MSA, a matomedinlike factor that was first described as the prodt of a rat liver cell line grown in serum-free medium. Pants with nonislet cell tumors and hypoglycemia have been reported to have elevated serum levels of MSA-like material whose nonsuppressible insulinlike activity accounts for the hypoglycemia. A variety of other cells also manufacture growth factors. For example, a line of BHK cells transformed by simian virus 40 produces a factor that stimulates the growth and movement of 3T3 cells. Growth factors have also been found in medium conditioned by L929 cells; these include nerve growth factor, a colony stimulating factor that is identical to macrophage growth factor, and other unidentified growth factors. Cells that synthesize ectopic growth factors, make new hormone receptors, or induce fresh blood supply through the synthesis of tumor angiogenesis factor may gain a selective advantage over their normal counterparts. Ectopic protein synthesis could then play a vital part in the growth and development of many types of tumors. (25 refs)

78-5453 **Developmental Potency of Normal and Neoplastic Cells of the Early Mouse Embryo.** (Eng) Gardner, R. L. (Dept. Zoology, Univ. Oxford, Oxford, England). *Excerpta Med Int Congr Ser* (432): 154-166; 1978.

Recent studies of the potency of normal early mammalian embryo cells and their neoplastic counterparts are reviewed along with studies of X inactivation, and some of the implications of this work are considered. Teratocarcinomas develop from both male and female germ cells in mice, and they can be produced by grafting early embryos ectopically in syngeneic adult hosts. This review is restricted to studies of the potency of the embryonal carcinoma stem cells (EC cells) of these tumors by blastocyst injection. So far, such transplantations have been carried out only with EC cells of embryo-derived teratocarcinomas, both from in vivo-passaged tumors and in vitro cultures. The results of these experiments demonstrate that EC cells from both sources can participate in embryogenesis and exhibit normal differentiation in a wide variety of organs and tissues of the conceptus and postnatal mouse. The range of normal cell types formed by EC cells in chimeras exceeds that found in both the tumors and in culture and has included functional spermatozoa in one instance. Most chimeras produced by injecting groups of cultured EC cells into blastocysts also developed tumors that invariably contained cells of donor origin. In single cell injection experiments, the EC cell clone in one animal autopsied at 4 wk postpartum had colonized every somatic organ and tissue tested. Several studies show that EC cells can retain their totipotency despite in vivo passage for several years, with or without an additional period of months in culture. EC Cells may correspond to cells of the germ line that require totipotency precociously as a consequence of disruption of embryonic organization through ectopic grafting. Studies of injecting EC cells into blastocysts also furnish an example of reversal of neoplasia in animal cells. However, it remains to be seen whether teratomas and teratocarcinomas represent special cases or whether conditions can be found that will

enable normal growth and differentiation of stem cells from other types of neoplasms to occur. (84 refs)

78-5454 **Growth of Human Tumor Cells in Established Cultures.** (Eng) Sinkovics, J. G. (Section Clinical Tumor Virology and Immunology, Dept. Medicine, M. D. Anderson Hosp. and Tumor Res. Inst., Univ. Texas System Cancer Center, Houston, TX, 77030); Gyorkey, F.; Kusyk, C.; Siciliano, M. J. *Methods Cancer Res* 14: 243-323; 1978.

Experience with the growth of human neoplastic cells in established cultures is reviewed. In 75% of the primary cultures set, groups of cells deemed to be neoplastic were observed, but only a small number of these cultures developed into established neoplastic cell lines. Sarcomas, carcinoma, and malignant melanoma cell lines are considered. The morphology and ultrastructure of the cell lines are illustrated in numerous figures, and some of the characteristics of each line (highest cell passage attained; morphology; patient's age, gender, race, and blood group; and verified tissue diagnosis of tumor-yielding cell line) are tabulated. Methods for characterizing established tissue cultures include determination of generation time and growth kinetics, cloning, karyotypic and chromosome banding, enzyme electrophoresis, and growth in immunosuppressed or immunoincompetent animals. The major aims of working with human tumor cell lines should remain (1) the representation of each human tumor category by several established cell lines for extensive laboratory studies and (2) the achievement of technical and procedural advances in the yield of established cell lines. (176 refs)

78-5455 **Genetics of Neoplasia--Impact of Ecogenetics on Oncogenesis. A Review.** (Eng) Purtilo, D. T. (Dept. Pathology, Univ. Massachusetts Medical Sch., 55 Lake Ave. N., Worcester, MA, 01505); Paquin, L.; Gindhart, T. *Am J Pathol* 91(3): 607-688; 1978.

The basic genetic mechanisms responsible for neoplasia are reviewed to guide the clinician in the differential diagnosis of inherited neoplastic syndromes. Particular attention is focused on the role of ecogenetics, the long-term variable effects of the environment on the genome, in the development of cancer. The specific topics include the mutational theory of oncogenesis, chromosome aberrations, marker chromosomes, clastogenic syndromes, the association of mutagenesis with teratogenesis and oncogenesis, familial cancer syndromes, the X-linked lymphoproliferative syndrome as a model demonstrating the impact of ecogenesis on oncogenesis, and the diagnosis of familial cancer syndromes. The familial cancer syndromes discussed include genodermatoses, neurofibromatosis, multiple endocrine neoplasia, familial CNS tumors, familial colon carcinoma, breast carcinoma, lung carcinoma, urinary system carcinomas, and familial hematopoietic malignancies. A medical history questionnaire for lymphoproliferative study is appended. (410 refs)

78-5456 **Highlights of Neurosurgery in Nigeria.** (
Adeloye, A. (Dept. Surgery, Univ. Ibadan,
dan, Nigeria). *Trop Geogr Med* 29(4): 325-334; 1977.

The major types of neurological operations performed in
eria are reviewed. In Ibadan, the incidence of brain tu
is less than that seen among European communities.
male:female ratio is 5:1, and the patients are younger
those noted in a European series. The most common tu
are meningiomas and pituitary tumors; glioblastoma
tiforme is rare, and acoustic neuroma is virtually unkn
Approx 75% of the meningiomas are found in the co
region, the remainder in the basal region histologically,
of these tumors are of the syncytial type. The lesions d
the bulk of their blood from the internal carotid artery.
commonest pituitary tumor is the chromophobe adeno
Tuberculoma is one of the most important cause
space-occupying lesions. Burkitt's lymphoma affects
brain in about 60% of the cases and the brain, spinal c
and peripheral nerves in about 20% of the cases. The intr
nal canal tumor pattern in Nigeria does not differ mark
from that of other places. One interesting lesion found
intramedullary spinal cord schistosomal granuloma du
Schistosoma hematobium. Malignant trophoblastic di
involves the nervous system in about 12% of the cases.
cinoma of the thyroid gland is the commonest sourc
metastases to the skull in Nigeria. Metastatic tumors o
brain carry a 4:1 female:male incidence; the most freq
source of secondary tumor is choriocarcinoma. (41 refs

78-5457 **Nelson's Syndrome: Chickens, Eggs, and S
Explosions.** (Eng) Conomy, J. P. (Cleve
Clinic Foundation, 9500 Euclid Ave., Cleveland,
44106). *Arch Intern Med* 138(5): 691-692; 1978.

The origin of pituitary tumors in Nelson's syndrome is
cussed. The sequence and tempo of the illness usually co
of hyperadrenal corticism, adrenalectomy, progressive
hyperpigmentation, and pituitary tumor; the pituitary tu
may follow the adrenal extirpation by many months or y
Studies have indicated that the incidence of this syndr
in postadrenalectomy patients is 10%. Inferential clinical
dence suggests that, most frequently, removal of the adr
tumor is followed by development of the pituitary tumo
one series the reverse sequence is less common: < 3
the 120 patients undergoing surgical treatment of hy
adrenalcorticism were known to have a preexis
pituitary tumor. Of the 8% to 40% of postadrenalecto
patients in whom pituitary tumors are manifested,
are known to have any pituitary tumors to begin w
The pituitary tumors that do develop are prone to en
explode, and compress parasellar structures. One st
indicated that half the patients with postadrenalecto
pituitary tumors had an abnormal sella turcica and th
of these had an acute symptomatic necrotic disrup
of the tumor. (8 refs)

5458 **Genetically Susceptible Subgroups.** (Eng) Strong, L. C. (Graduate Sch. Biomedical ences, Univ. Texas Health Science Center at Houston, uston, TX, 77025). *Environ Health Perspect* 22: 139-140; 8.

orders characterized by chromosomal instability or inased mutagenesis in vivo or in vitro may predispose to lignancy. These disorders include xeroderma pigmenum, Fanconi's anemia, Bloom's syndrome, and ataxia ngiectasia. There may be a genetically determined inased risk of mutation and cancer following exposure to tain environmental agents as a result of a genetically deterned metabolism of that particular agent. If malignancy is result of sequential mutations, susceptible subgroups ght include all individuals who have sustained a primary tation through a germinal or somatic cell. Individuals who erit the predisposing mutation are at greatest risk because ch cell of the sensitive tissue carries the mutant gene, and ubsequent mutation in any cell may lead to malignancy. e sequential mutation model also accounts for the synergic, multiplicative effects of mutagens on the risk of cancer general. Promotional factors may be critical in the probaity of cancer in individuals who acquire the first mutation a somatic cell. Study of uniquely susceptible subgroups ay contribute to an understanding of carcinogenesis in genl. (no refs)

-5459 **Genetics and Cancer in Children.** (Eng) Lynch, H. T. (Dept. Preventive Medicine and Public ealth, Creighton Univ. Sch. Medicine, Omaha, NB); ynch, P. M. *Pediatr Ann* 7(6): 71-93; 1978.

he influence of primary genetic events, radiation, congenital rth defects, environmental interactions, and cytogenetic errations in familial childhood cancer is discussed. The delopment of a national registry of cancer-prone families is commended as an aid to the study, management, and conol of high-risk children. (80 refs)

8-5460 **Breast Cancer Morbidity and Mortality in the Soviet Union.** (Rus) Merabishivili, V. M. (N. N. etrov Res. Inst. Oncology, Leningrad, USSR); Dymarskii, . Iu. *Vopr Onkol* 24(8): 3-9; 1978.

ndices of morbidity and mortality due to malignant breast umors in the Soviet Union are reviewed. Breast cancer morbidity increased from $8.4/10^5$ in 1960 to $12.5/10^5$ in 1975; orrespondingly, the mortality index increased from $.9/10^5$ to $6.4/10^5$. The absolute number of patients with breast cancer increased by 36.9% from 1970 to 1975 and it reached 177,469. (16 refs.)

78-5461 **Epidemiology of Cervical Cancer.** (Ger) Berndt, H. (Klinik fur innere Medizin, Bezirkskrankenhaus, Dr. Wilhelm-Kulz Strasse, Postfach 480, DDR-20 Neubrandenburg, E. Germany); Neuser, D. *Arch Geschwulstforsch* 48(3): 250-275; 1978.

Differences in cervical cancer incidence and mortality between countries, the known risk factors in the disease, and East Germany's preventive control program are reviewed. The importance of treating preneoplastic lesions (dysplasia and carcinoma in situ) is emphasized. (262 refs)

78-5462 **HLA System and Malignant Diseases.** (Fre) Feingold, N. (Group de Recherches de Genetique epidemiologique, INSERM, U.155, Chateau de Longchamp, Bois de Boulogne, F75016 Paris, France). *Bull Cancer (Paris)* 65(1): 79-82; 1978.

Investigative work in the last 10 yr on the possible association of antigens of the major histocompatibility system (HLA) and malignant disease is reviewed. There is some evidence for the association of antigens B5, B15, B18, BW35, and A1 with Hodgkin's disease. Antigens A2 and B12 appear to be associated with acute lymphoblastic leukemia. Except for the association of Sin2 and nasopharyngeal cancer, there is no statistical support for an association of specific HLA antigens and solid tumors. Intrapopulation studies show that the incidence of some cancers may follow the incidence of certain HLA antigens. These coincident cancer and HLA patterns may indicate a factor of susceptibility or resistance to cancer in a particular population. (16 refs)

78-5463 **Epidemiological Outlook on Cancer.** (Eng) Curnen, M. G. (Sch. Public Health, Columbia Univ., 600 W. 168th St., New York, NY, 10033). *Bull NY Acad Med* 54(4): 349-365; 1978.

An epidemiological overview of cancer incidence in the US is presented. The most common cancers in men are those of the lung, colon and rectum, and prostate; the most common in women are those of the breast, colon and rectum, and lung. Survival rates of these and other major cancers indicate that only cancers of the colon and rectum, lung, and pancreas have 5-yr survivals of $<50\%$. Most cancers appear to be linked to environmental pollutants. (10 refs)

78-5464 **Experimental Studies on the Carcinogenicity of Bracken Fern (*Pteridium aquilinum*) in the Rat.** (Jpn) Kato, T. (First Dept. Pathology, Sch. Medicine, Gifu Univ., Tsukasa-cho, Gifu 500, Japan). *Gifu Daigaku Igakuba Kiyo* 26(2): 318-333; 1978.

The carcinogenicity of bracken fern (*Pteridium aquilinum*) was determined in feeding experiments in ACI rats. Three groups of rats received a diet containing 5%, 10%, and 30% bracken, respectively, for 60 days and three groups received the corresponding diets for 480 days. Most of the resulting tumors were adenomas and adenocarcinomas of the ileum, and the commonest site was the terminal 20 cm of the ileum, particularly the terminal 3-cm section nearest the ileocecal junction. Ileal sarcomas and urinary bladder carcinomas were infrequent. For the three dose groups, rats treated for 60 days had tumor incidences of 11.1%, 25.0%, and 56.2%, respectively; rats treated for 480 days had incidences of 38.4%, 93.3%, and 92.8%. Tumor multiplicity was dose-related. The intestine was much more susceptible than the urinary bladder to the carcinogenicity of bracken: a > 10% bracken diet for 480 days was necessary for the induction of urinary bladder tumors. Atypical hyperplasia of the small intestinal mucosa usually appeared 14 wk after the start of the bracken diet. After about 28 wk, the frequency of atypical hyperplasia was reduced and the adenomas and adenocarcinomas became prominent. (18 refs)

78-5465 **Carcinogenicity of Boiling Water Extract of Bracken, *Pteridium aquilinum*.** (Eng) Hirono, I. (Dept. Carcinogenesis and Cancer Susceptibility, Inst. Medical Science, Shiroganedai 4-6-1, Minato-ku, Tokyo 108, Japan); Ushimaru, Y.; Kato, K.; Mori, H.; Sasaoka, I. *Gann* 69(3): 383-388; 1978.

The carcinogenicity of an aqueous extract of bracken fern (*Pteridium aquilinum*) was studied in inbred ACI rats. In experiment I, Group 1 rats received a diet containing unprocessed dry bracken powder for 3 mo; Group 2 received a boiling water extract of dry bracken as drinking water for 16 mo; Group 3 received a cold water extract of dry bracken as drinking water for 16 mo; and Group 4 received a diet containing a concentrated boiling water extract of dry bracken for 16 mo. Rats in experiment II received a diet containing a concentrated boiling water extract of dry bracken, for 500 days. A control group was fed a normal diet. Most of the Group 1 animals developed multiple ileal tumors, such as adenomas and adenocarcinomas. In Group 2, 6/11 rats that survived > 7 mo developed tumors in the ileum and/or the urinary bladder. Group 3 rats had no tumors. In Group 4 and experiment II rats, all animals except one in experiment II had urinary bladder tumors, and almost all the rats in th groups also had ileal tumors. These results show that carcinogen in bracken fern is extractable in boiling water. refs)

78-5466 **Mycotoxin Mutagenesis--Mutagenic Activity Some Species of Subarctic Grain Fungi (Me ing Abstract).** (Eng) Sorsa, M. (Dept. Genetics, Univ. Hels ki, Helsinki, Finland); Linnainmaa, K.; Ilus, T. *Mutat* 53(2): 267; 1978. (1 ref)

78-5467 **Mitotoxicity of β-Exotoxin and δ-Endoto Protein from *Bacillus thuringiensis* (Meet Abstract).** (Eng) Sahu, R. K. (Cytogenetics Lab., Berham Univ., Berhampur 760 007, Orissa, India); Panda, B. Sharma, C. B. *Mutat Res* 53(2): 256-257; 1978. (no refs)

78-5468 **Induction of Renal and Hepatic Tumors in M by Ochratoxin A, a Mycotoxin.** (Eng) Kani wa, M. (Dept. Pathology, Tokyo Metropolitan Inst. Gero tology, 35-2 Sakae-cho, Itabashi-ku, Tokyo 173, Japa Suzuki, S. *Gann* 69(4): 599-600; 1978.

Ochratoxin A (Och A), a mycotoxin produced by *Aspergil* and *Penicillium*, was found to have a carcinogenic effect the liver and kidney of ddY mice, and this effect was e hanced synergistically by the presence of aflatoxin (AFB_1). Mice were divided into six groups and giv Och A (40 ppm of diet), AFB_1 (20 mg/kg by gast intubation), dimethyl sulfoxide (DMSO: 0.1 mg/20 g gastric intubation), Och A + AFB_1, Och A + DMSO, no treatment. Och A produced 1 hyperplastic nodule the liver, 5 hepatic cell tumors, 4 atypical kidney tubul 9 cystic adenomas, and 2 renal cell tumors among mice. AFB_1 produced 1 hyperplastic nocule, 2 hepa cell tumors and 1 cystic adenoma among 18 mice. Och AFB_1 produced 8 hyperplastic nodules, 15 hepatic c tumors, 11 atypical tubules, 19 cystic adenomas, and renal cell tumors among 20 mice. The renal cell tumc appeared to be of epithelial cell origin, corresponding Grawitz tumors in humans; the hepatic tumors we well-differentiated trabecular adenomas. (2 refs)

78-5469 **Action of Dihydroaflatoxins on Rat Liver Mit chondria. I. Membrane-dependent Osmotic ar**

x Effects of Aflatoxins B_2 and G_2. (Eng) Obidoa, O. t. Biochemistry, Univ. Nigeria, Nsukka, Nigeria); Babaıi, E. A.; Bassir, O. *Toxicology* 11(1): 29-36; 1978.

many fungal-coumarin metabolites can inhibit rat liver chondria, it is suggested that aflatoxin B_2 (AFB_2) and oxin G_2 (AFG_2) possess similar activity that may partialcount for their toxicity. Therefore, the membrane-deent osmotic and redox effects of the two dihydroaflatoxn isolated rat liver mitochondria were investigated. At thal yet carcinogenic doses (1-2 x 10^{-6} M). Both comds had no deleterious effect on the permeability of the chondrial membrane. They did not cause any marked ling, inhibit any ATP-induced contraction or stimulate chondrial ATPase activity. These findings are signifi because reversible changes in the permeability of mitodrial membranes are important in the regulation of cel metabolic activity. The toxins were capable of inhibiting ron transport terminally, between cytochrome c and gen (cytochrome oxidase). The significance of these findin relation to the differential toxicity of the aflatoxins scussed. (23 refs)

5470 **Influence of Dietary Protein and Vitamin B_{12} on the Toxicity and Carcinogenicity of Aflatoxin Rat Liver.** (Eng) Temcharoen, P. (Dept. Pathobiology, ulty Science, Ramathibodi Hosp., Mahidol Univ., Bang, Thialand); Anukarahanonta, T.; Bhamarapravati, N. *ıcer Res* 38(7): 2185-2190; 1978.

influence of dietary protein content and dietary vitamin supplement on the hepatotoxicity and carcinogenicity of toxins (a mixture of aflatoxins B1 and G1, with trace ounts of B2 and G2) in rat liver was studied. In rats fed w-protein diet (5% casein), the aflatoxin mixture (1 ppm) he diet induced extensive toxic and carcinogenic effects. rhosis was significantly prevented by vitamin B_{12} adminision (5 μg/100 g diet), but the incidence of cholangiofibroand hyperplastic nodules was unchanged. No toxic effect observed in rats receiving a high-protein diet (20% ca) with no vitamin B_{12} supplement for the 33 wk duration study. Only one rat bearing a hepatoma was observed ong 25 rats receiving the high-protein diet with no vitamin supplement, whereas 6 hepatomas and 4 hyperplastic lules were seen among 25 rats receiving the high-protein t plus vitamin B_{12}. Cholangiofibrosis and cirrhosis were observed in the high-protein groups, regardless of vitamin administration. The above observations and those of oth suggest that vitamin B_{12} may potentiate some chemical rcinogens in the induction of biochemical derangements d the initiation of tumor formation. (63 refs)

-5471 **A Diploid Rat Liver Cell Culture. IV. Malignant Transformation by Aflatoxin B_1.** (Eng) Schaeffer, W. I. (Dept. Medical Microbiology, Coll. Medicine, Univ. Vermont, Given Medical Building, Burlington, VT, 05401); Heintz, N. H. *In Vitro* 14(5): 418-427; 1978.

Cloned rat hepatocyte cultures (RL-PR-C) were chronically exposed to a subtoxic, sublethal dose of aflatoxin B_1 (AFB): 0.5 μg/ml AFB was administered to the cultures at each weekly passage beginning at passage 12. Continuous exposure to AFB increased the tumorigenic potential of the RL-PR-C cells, as tested by back-injection into isogeneic animals. Control cultures exhibited spontaneous transformation at passage 56, about 20 passages beyond the chemically induced event. Neither AFB-treated nor control cultures exhibited cytopathological morphology, formation of cell foci, growth in soft agar, or irregular fibroblastlike growth patterns that could be specifically related to the onset of tumorigenic potential. Karyotypic analysis revealed no specific chromosomal aberrations associated with AFB treatment; however, chromosomal instability was a property of the tumorigenic cell populations. Injection of both AFB-treated and control cultures at passage 56 into isogeneic newborn Wistar/Lewis rats resulted in tumors indicative of both carcinoma and sarcoma, demonstrating the multipotency of these epithelial cells transformed in vitro. The microenvironment at the location of the injected cells might dictate the ability of the cells to form tumors and may affect the morphology of the resultant tumors. The results suggest that it will be necessary to examine biochemical rather than morphological differences when monitoring epithelial cells for transformational events. (19 refs)

78-5472 **The Major Metabolite of Aflatoxin B_1 in the Rat Is a Glutathione Conjugate.** (Eng) Degen, G. H. (Institut fur Pharmakologie und Toxicologie, Universitat Wurzburg, Verbacher Landstrasse 9, 8700 Wurzburg, W. Germany); Neumann, H. G. *Chem Biol Interact* 22(2/3): 239-255; 1978.

The water-soluble, nonextractable metabolites of aflatoxin B_1 (AFB_1) were characterized in vivo and in vitro. When ^{14}C-AFB_1 was injected ip into female Wistar rats (0.5 or 2.5 mg/kg), 60%-65% of the dose was eliminated into the bile, mostly as polar, nonextractable metabolites. A glutathione conjugate was the major metabolite produced. This conjugate was also formed when a rat liver postmitochondrial supernatant was incubated with AFB_1 and ^{3}H-glutathione. The conjugate was purified by ion-exchange, gel-filtration, and thin-layer chromatography. It was tentatively identified as 2,3-dihydro-2-(S-glutathionyl)-3-hydroxy aflatoxin B_1. This structure was derived mainly from amino acid analysis, UV spectra, and the enzymatic requirements for its formation in vitro. In the rat, this detoxification product of the potentially ultimate reactive AFB_1 epoxide constitutes about 10% of the administered dose and, thus, underlines the quantitative importance of this activation pathway. The toxicity of AFB_1 should largely depend on the relative rates of the epoxidation and glutathione conjugation reactions, as these rates deter-

mine the degree of exposure of tissue to the ultimate reactive form. (36 refs)

78-5473 **Dietary Lipotropes, Hepatic Microsomal Mixed-Function Oxidase Activities, and In Vivo Covalent Binding of Aflatoxin B_1 in Rats.** (Eng) Campbell, T. C. (Div. Nutritional Sciences, Cornell Univ., Ithaca, NY, 14853); Hayes, J. R.; Newberne, P. M. *Cancer Res* 38(12): 4569-4573; 1978.

Studies were carried out to determine whether the increased susceptibility of rats to aflatoxin B_1 (AFB_1) hepatocarcinogenesis when they were fed a high-fat diet deficient in lipotropes could be related to the mixed-function oxidase (MFO) metabolism of AFB_1. Weanling male Sprague-Dawley rats were fed a nutritionally complete synthetic diet or a diet marginally deficient in choline and methionine and lacking folacin for 97-100 days. Hepatic microsomal MFO activities, as assayed by ethylmorphine N-demethylation, ethoxycoumarin O-dealkylation, and cytochrome c reduction, were depressed to a similar extent (21%-39%) by the lipotrope-deficient (LD) diet, when expressed on a microsomal protein basis. In addition, cytochrome P-450 content was reduced by 37%, and AFB_1 metabolism was lowered slightly. The proportion of an ip dose of AFB_1 (1 mg/kg) that became covalently bonded to DNA and RNA was reduced to a similar extent by the LD diet 6 hr after injection, but the formation of AFB_1-protein adducts was not affected. The depression of DNA and RNA adduct formation in the animals that received the LD diet was probably related to the lower MFO activities and not to an alteration of glutathione levels, which remained unchanged by dietary treatment. These results suggest that the marginally LD diet does not enhance tumor formation through an increased microsomal activation of AFB_1. (37 refs)

78-5474 **Binding of Aflatoxin to DNA as Studied by Optical Detection of Magnetic Resonance.** (Eng) Kwiram, A. L. (Dept. Chemistry, Univ. Washington, Seattle, WA, 98195); Liu, Y. C.; Farquhar, M. N.; Smuckler, E. A. *Biochem Biophys Res Commun* 83(4): 1354-1359; 1978.

The binding of aflatoxin B_1 (AFB_1) to intact DNA was studied by optical detection of magnetic resonance (ODMR) using both in vitro and in vivo samples. For the in vivo experiments, rats were injected with 10 μg/kg AFB_1 bid for 2 days, and DNA was subsequently extracted from the liver. The in vitro studies used DNA-AFB complexes formed in microsomal preparations. ODMR measurements were carried out for free AFB_1 and AFB_2, for the reaction-DNA sample, and for solns of native DNA to which either AFB_1 (designated DNA/AFB_1) or AFB_2 (DNA/AFB_2) had been added. The wavelength-dependent data showed that there is a small but distinct difference between AFB_1 and AFB_2. The results for DNA/AFB_1 and DNA/AFB_2 were essentially the same those for free AFB_1 and AFB_2. However, the reaction-D data coincided with the data for AFB_2, which was the m for covalently bound AFB_1. The small shift in ODMR tra tion frequencies is consistent with the view that binding curs at the furofuran ring, since derivatization in the arom region of the molecule or at the keto groups would hav substantially larger effect than that observed. The differe in the data for AFB_2/DNA and the reaction-DNA sam supports the view that aflatoxin is covalently bound and merely a physically bound AFB_2 metabolite. (20 refs)

78-5475 **The Induction of Sister-Chromatid Exchan in Chinese Hamster Ovary Cells by Prolon Exposure to 2-Acetylaminofluorene and S-9 Mix.** (E Takehisa, S. (Lab. Radiobiology, Univ. California, San Fr cisco, CA, 94143); Wolff, S. *Mutat Res* 58(1): 103-106; 19

When the time of treatment of Chinese hamster ovary c with 2-acetylaminofluorene plus S-9 mix (rat liver crosomes supplemented with an NADPH-generating syst was extended from 0.5 to 2.5 hr, the yield of sister chroma exchanges was approx doubled. (19 refs)

78-5476 **The Effects of Discontinuing Administration High Levels of 2-Acetylaminofluorene on Transitional Epithelium of the Mouse Urinary Bladd** (Eng) Frith, C. H. (Pathology Services Project, Natl. Cen Toxicological Res., Jefferson, AR, 72079); Rule, J. E. *J E ron Pathol Toxicol* 1(5): 581-585; 1978.

The effects of discontinuing the administration of a high le of 2-acetylaminofluorene (2-AAF) on the transitional e thelium of the urinary bladder were studied in BALB/c mi A group of 288 mice was given 500 ppm 2-AAF in the d for 6 wk, and subgroups of 96 were killed at 6, 13, and wk. Another group of 288 mice was given the same dose 2-AAF for 13 wk, and subgroups were killed at 13, 26, a 39 wk. Hyperplasia of the transitional epithelium was pres in 99% and nodular downgrowths of transitional epitheli into the lamina propria were present in 22% of the anim sacrificed at 6 wk. Seven weeks after withdrawal of the c cinogen, the incidence of both hyperplasia and nodular dow growths had decreased to 4%. Twenty weeks after carcinog removal, hyperplasia was present in 5% of the animals, b nodular downgrowths were absent. A similar pattern w seen in animals treated for 13 wk, but the urothelial hyp plasia regressed at a slower rate. Four mice sacrificed at wk had small transitional cell carcinomas. At 39 wk, 26 after discontinuing 2-AAF, hyperplasia was still present 17% of the animals and transitional cell carcinomas we found in 2%. The results suggest that exposure to a high le of carcinogen even for a relatively brief period may result

levelopment of carcinomas after the cessation of expo- (10 refs)

477 **DNA Repair in Primary Cultures of Rat Hepatocytes.** (Eng) Yager, J. D. (Dept. Patholo- Dartmouth Medical Sch., Hanover, NH, 03755); Miller, . *Cancer Res* 38(12): 4385-4394; 1978.

A repair was analyzed quantitatively in cultured Wistar hepatocytes following exposure to UV light, etylaminofluorene (AAF), and its derivatives N-hy- xy-2-acetylaminofluorene (N-OH-AAF) and N-ace- -2-acetylaminofluorene (N-Ac-AAF). The nuclear hymidine (^{3}H-dThd) labeling index of control cultures less than 0.1%, but significant cytoplasmic labeling was ent in autoradiographs. Of the total acid-precipitable oactivity present in control cultures, 54% of the ^{3}H was d in protein, demonstrating the ability of these nonre- ating hepatocytes to catabolize ^{3}H-dThd and reutilize the led metabolites. UV light irradiation of the cultured atocytes resulted in a dose-dependent increase of ^{3}H-dThd rporation into DNA. That this represented nuclear DNA ir synthesis was demonstrated by detecting nonsemicon- ative DNA synthesis (repair replication) with NaI iso- nic centrifugation and autoradiography. Hydroxyurea and 100 mM) had only a small inhibitory effect, but 1- D-arabinofuranosylcytosine (25 and 100 μM) and ethidi- bromide (25 μM) dramatically inhibited the UV-induced ease in ^{3}H-dTHd incorporation. Repair synthesis also oc- red in response to treatment with AAF, demonstrating the ity of the hepatocytes to metabolize this prohepatocar- gen to a form capable of damaging DNA. N-OH-AAF N-Ac-AAF were more effective in inducing a repair re- nse. These results demonstrate the usefulness of primary atocyte cultures for studies of carcinogenesis and as a eening system for environmental chemicals suspected of naging DNA and causing cancer. (49 refs)

5478 **Effect of 3-Methylcholanthrene Pretreatment on 2-Acetylaminofluorene N- and Ring-Hy- xylation by Rat and Hamster Liver Microsomes.** (Eng) likar, P. D. (Fels Res. Inst., Temple Univ. Med. Sch., ladelphia, PA, 19140); Hong, Y. S.; Baldy, W. J. *Toxicol t* 2(3): 135-139; 1978.

e effect of pretreatment with 3-methylcholanthrene (MC) or to sacrifice of rats and hamsters on the ability of liver crosome preparations to induce N- and ring-hydroxyla- n of 2-acetylaminofluorene (AAF) was investigated. hydroxylation of AAF has been established as an activa- n step in the latter compound's carcinogenic effect, and g-hydroxylation is considered to be an inactivation step. C, 100 mg/kg body wt, was injected ip into male Sprague wley rats and male Syrian golden hamsters 24 hr before death. Liver microsome fractions were incubated with either 2.3 or 100 θM AAF, and results were expressed in nanomoles of hydroxy-AAF formed/30 min per nanomol of cytochrome P-450 or P-448. Rats pretreated with MC had a significant ($p < 0.05$) increase in both N- and ring-hydroxylation for low and high concentrations of AAF. Pretreatment of hamster with MC induced a specific and large increase ($p < 0.05$) in N-hydroxylation only. In rats, it has been shown that simultaneous administration of MC and AAF inhibits liver tumor induction. Liver carcinogenicity by AAF in hamsters is not inhibited by treatment with MC. The in vitro results of this study are discussed in relationship to these in vivo studies. (21 refs)

78-5479 **In Vitro Binding of 2-Acetaminofluorene to RNA and Protein with Rat Liver Microsomes.** (Eng) Hara, E. (Biochemistry Div., Saitama Cancer Center Res. Inst., Ina-Machi, Kitaadachi-gun, Saitama-ken 362, Japan); Yonekawa, H.; Kawajiri, K.; Masuda, A.; Tagashira, Y. *Gann* 69(4): 533-538; 1978.

The binding of 2-acetylaminofluorene (AAF) with exogenous Torula yeast RNA and endogenous protein was studied in vitro in a Sprague-Dawley rat liver microsome system. The covalent binding of ^{14}C-labeled AAF with RNA and microsomal protein depended on the concentration of AAF or microsomes and increased linearly with time up to 45 min. AAF bound to protein 100 times more readily than to RNA. The enhancement of binding by methylcholanthrene treatment, its inhibition by 7,8-benzoflavone, and the requirement for NADPH suggested that mixed-function oxidases were involved in the reaction. The binding of AAF was not due to cytosol contamination in the microsomal fraction. In fact, addition of cytosol or the cofactors ATP and sulfate ion suppressed the binding to both RNA and protein. N-Hydroxy-2-acetylaminofluorene, a mixed-function metabolite of AAF, contributed only 1.74% of the binding to RNA and 0.39% of the binding to microsomal protein. A ring-hydroxylated metabolite may be responsible for most of the binding. (21 refs)

78-5480 **Use of Intact Liver Cells for Metabolic Activation in a Simplified Fluctuation Test for Detection of Carcinogens and Mutagens (Meeting Abstract).** (Eng) Hubbard, S. A. (Dept. Biochemistry, Univ. Surrey, Surrey, England); Bridges, J. W.; Green, M. H.; Bridges, B. A. *Mutat Res* 53(2): 202; 1978. (1 ref)

78-5481 **Enhancing Effect of Chemicals on Production of Hyperplastic Liver Nodules Induced by N-2-Fluorenylacetamide in Hepatectomized Rats.** (Eng) Ito,

N. (First Dept. Pathology, Nagoya City Univ. Medical Sch., 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467, Japan); Tatematsu, M.; Hirose, M.; Nakanishi, K.; Murasaki, G. *Gann* 69(1): 143-144; 1978.

A comparison was made of the effects of various inducers of drug-metabolizing enzymes on the production of hyperplastic nodules in the livers of partially hepatectomized rats that had been treated with N-2-fluorenylacetamide (2-FAA). Male Fischer rats were maintained for 2 wk on a diet containing 200 ppm 2-FAA. Some animals were then maintained for 8 wk on diets containing 1,000 ppm polychlorinated biphenyl (PCB), 500 ppm phenobarbital, 2,500 ppm 3-(3,5-dichlorophenyl)-5,5-dimethyloxazoline-2,4-dione (DDOD), or 500 pm phenobarbital plus 500 ppm β-naphthoflavone; controls were maintained on the 2-FAA diet for these 8 wk. The incidence of hyperplastic nodules in the livers of animals partially hepatectomized during the third week was highest in the group fed PCB, decreasing sequentially in the animals fed phenobarbital, phenobarbital plus β-naphthoflavone, and DDOD. In all cases, the incidence was significantly higher than that in animals fed 2-FAA only. The hyperplastic nodules were generally < 1.5 mm in diameter in all groups. This system may prove to be a valid in vivo short-term screening test for hepatocarcinogens. (11 refs)

78-5482 **Effects of 2-Acetylaminofluorene on Diurnal Oscillations in Nucleic Acid Metabolism in Two Classes of Nuclei Isolated from Rat Liver.** (Eng) Bushnell, D. E. (Dept. Pathology, Veterans Admin. Hosp., 150 Muir Drive, Martinez, CA, 94553); Jeter, J. R. *Cancer Res* 38(8): 2533-2538; 1978.

The effects of 2-acetylaminofluorene (AAF) on the diurnal fluctuations in nuclear nucleic acid labeling from pyrimidine precursors were investigated. ARS/Sprague-Dawley rats were fed a 60% protein diet with or without 0.028% AAF for 5 wk, on an 8 + 16 feeding schedule (AAF was given only during the first 8 hr of a 12-hr dark period). Liver nuclei were pulse-labeled (P-L) for 2 hr with ^{3}H-thymidine and ^{14}C-orotic acid three times during the feeding-lighting schedule, and isotope incorporation into DNA and RNA was determined. To do this, nuclei were fractionated into two classes, N-1 and N-2. In control livers, hepatocyte nuclei were found primarily in the N-1 class, stromal nuclei in the N-2 class. P-L of control liver nuclear DNA (nDNA) revealed that labeling peaked 2-4 hr after the feeding period. In treated livers, the N-2 population increased significantly during AAF feeding, apparently as the result of a shift of hepatocyte nuclei in AAF-fed rats reached a higher level than that in controls; however, the labeling did not peak, and there was a large variation in labeling from animal to animal at individual pulse periods. In controls, P-L of nRNA peaked 4-6 hr after the start of feeding, but RNA labeling in both nuclei classes from AAF-fed animals did not peak during the times examined. In addition, there was little variation among individual rats. The results suggest that feeding AAF to alters nuclear nucleic acid metabolism in most liver c Changes in liver enzyme composition may be related to alterations in liver nRNA metabolism in AAF-fed anim Presumably, alteration of nuclear structure and func could explain the changes in the regulation of gene expres found in hepatomas and precancerous liver. (32 refs)

78-5483 **Site of Origin of 2,7-FAA-induced Rat L kemia.** (Eng) Takayama, S. (Dept. Pathol Faculty Medicine, Tokyo Medical and Dental Univ., shima 1-5-45, Bunkyo-ku, Tokyo 113, Japan); Fujiwara, *Acta Pathol Jpn* 28(4): 531-539; 1978.

The primary site of mature granulocytic leukemia (M was compared with that of erythroblastic leukemia (EL Wistar and Sprague-Dawley rats, in which leukemia was duced by N,N'-2,7-fluorenylenebisacetamide (2,7-F 0.025% of diet). The appearance of orthochromatic erythr lasts in the peripheral blood was used as an index of the in stage of leukemia. Most animals were sacrificed when number of erythroblasts appeared. In addition, almost bones were examined histologically. Nodular foci of solit lesions and conspicuously large foci of scattered lesions w considered to be the primary site of leukemia. Leukemia induced in 151/356 Wistar rats and 27/74 Sprague-Daw rats, with the main types being MGL or EL. The foci peared mainly in the bone marrow of various bones. M of the MGL originated in the short bones, but most of EL originated in the long bones. Two cases of EL also or nated in the spleen. The difference in primary site betw MGL and EL was significant ($p < 0.001$). The short bo have abundant bony trabeculae in the shaft; the long bo have scanty bone trabeculae. Thus, the origin of MGL see to be connected with bone tissue, but that of EL seems to h little connection with this tissue. Morphologically, the M resembled human chronic myelogenous leukemia. (19 r

78-5484 **Hematogenous Development of Rat Mat Granulocytic Leukemia. Comparison 2,7-FAA-induced and Transplanted Leukemia.** (E Takayama, S. (Dept. Pathology, Faculty Medicine, To Medical and Dental Univ., Yushima 1-5-45, Bunkyo- Tokyo 113, Japan); Fujiwara, M. *Acta Pathol Jpn* 28 523-529; 1978.

In order to prove the hypothesis that mature granuloc leukemia (MGL) is spread by hematogenous metastasis fr nodular foci in the bone marrow to various organs of body, the degree of leukemic cell infiltration of N,N 2,7-fluorenylenebisacetamide (2,7-FAA)-induced MGL compared with that of transplanted MGL in Wistar rats. transplantation of leukemia exemplified hematogen metastasis. Group 1 rats were fed 2,7-FAA (0.025% of di

Group 2 rats were inoculated iv with 2 x 10^5 to 4 x 10^9 from eight Group 1 rats with MGL. MGL was induced 3/503 Group 1 rats and 67/318 Group 2 rats. (Morphoally, the MGL resembled human chronic myelogenous emia.) Hematologically and histologically, the leukemias ie two groups were similar. In both, the degree of leuia cell infiltration was similar, being high in the bone row, medium in the spleen, and low in the liver. The larity of infiltration between 2,7-FAA-induced and transted MGL suggests that the former is spread by hemanous metastasis from the primary nodular foci of the e marrow to various parts of the bone marrow, spleen, , and other organs. (14 refs)

5485 **Association of an Angiosarcoma of the Liver with a Hepatoma in a Vinyl Chloride Worker.** e) Delorme, F. (Centre Hospitalier Regional de la Mauri- C.P. 1130, Shawinigan-Sud, Quebec, Canada). *Ann Anat hol (Paris)* 23(2): 105-113; 1978.

1-yr-old man who had been exposed occupationally to yl chloride vapors for 23 yr, 4 mo died in a coma with ndice. Autopsy revealed the association of a hepatic angircoma with a hepatoma. Alcohol consumption by the pat was negligible. The association of the two tumors is the t ever to be reported in the literature. (22 refs)

5486 **Ten Cases of Angiosarcoma of the Liver in Vinyl Chloride Workers in Canada.** (Fre) Deme, F. (Centre Hospitalier Regional de la Mauricie, C.P. 0, Shawinigan-Sud, Quebec, Canada). *Ann Anat Pathol aris)* 23(2): 97-104; 1978.

n cases of hepatic angiosarcoma were found among emyees of a vinyl chloride plant in Shawinigan, Canada. All ients had been exposed to vinyl chloride vapors. The av e of the patients was 50 yr (41-61 yr); the length of occupanal exposure to vinyl chloride averaged 16 yr 10 mo (rang from 5 yr, 8 mo to 26 yr); and the time lapse between st exposure and diagnosis was 20.5 yr (11-18 yr). Survival er diagnosis averaged 4.4 mo (1-8 mo). The risk of hepatic giosarcoma appears to be highest among vat cleaners, pipe ters, and polymerization workers. (16 refs)

-5487 **Lack of Mutagenicity of Extracts from Polyethylene (PE) in Strains of *Salmonella typhimurium* (Meeting Abstract).** (Eng) Fevolden, S. E. (Cenl Inst. Industrial Res., Blindern, Oslo 3, Norway); Moller, E. *Mutat Res* 53(2): 186-187; 1978. (no refs)

78-5488 **External Chromosome Studies Undertaken on Persons and Animals with VC Illness (Meeting Abstract).** (Eng) Fleig, I. (Occupational Medicine and Health Protection, BASF, Aktiengesellschaft, 6700 Ludwigshafen, W. Germany); Thiess, A. M. *Mutat Res* 53(2): 187; 1978. (no refs)

78-5489 **Cytogenetic Investigations on Lymphocytes from Workers Exposed to Vinyl Chloride (Meeting Abstract).** (Eng) Leonard, A. (Mammalian Genetics Lab., C.E.N.-S.C.K., B-2400 Mol, Belgium); Decat, G.; Leonard, E. D. *Mutat Res* 53(2): 219; 1978. (no refs)

78-5490 **The Metabolic Activation of Vinyl Chloride In Vitro (Meeting Abstract).** (Eng) Ivanetich, K. M. (Dept. Physiology and Medical Biochemistry, Univ. Cape Town Medical Sch., Cape Town, South Africa); Katz, I. D.; Aronson, I. *Mutat Res* 53(2): 204; 1978. (no refs)

78-5491 **External Chromosome Investigations of a Person with an Angiosarcoma due to VC Exposure (Meeting Abstract).** (Eng) Fleig, I. (Arbeitsmedizin und Gesundheitsschutz, BASF, Aktiengesellschaft, 6700 Ludwigshafen, W. Germany); Thiess, A. M. *Mutat Res* 53(2): 187-188; 1978. (no refs)

78-5492 **Detection of Electrophilic Metabolites of Halogenated Olefins with 4-(4-nitrobenzyl)pyridine (NBP) or with *Salmonella typhimurium* (Meeting Abstract).** (Eng) Barbin, A. (Unit Chemical Carcinogenesis, International Agency for Res. on Cancer, 150 cours Albert Thomas, 69008 Lyon, France); Planche, G.; Croisy, A.; Malaveille, C.; Bartsch, H. *Mutat Res* 53(2): 150; 1978. (no refs)

78-5493 **Lung Tumorigenesis by 1,2-Diformylhydrazine in Mice.** (Eng) Toth, B. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, Omaha, NB, 68105); Erickson, J. *Z Krebsforsch* 92(1): 11-16; 1978.

Beginning at 6 wk of age, randomly bred Swiss albino mice (50 males and 50 females) were administered 1,2-diformylhydrazine (DFH: 2% soln in drinking water) over their entire life-span in order to determine the relative carcinogenicity of

mono- and dialkylhydrazines and also their possible environmental significance as carcinogens. The av daily intake of DFH was 144 mg for females and 146 mg for males. Of the females, 48 developed 467 lung tumors: 19 had 113 adenomas and 29 had 307 adenomas and 47 adenocarcinomas. Of the males, 41 developed 376 lung tumors: 26 had 154 adenomas and 15 had 189 adenomas and 33 adenocarcinomas. The av age at death of both males and females was 66 wk. In contrast, only 15/100 female controls developed 17 lung tumors and only 22/100 male controls developed 25 lung tumors. Although a few instances of other types of tumors were observed in various groups, their low incidences suggest that their appearance cannot be attributed to the treatment. (20 refs)

78-5494 **Strain Susceptibility and Resistance to 1,2-Dimethylhydrazine-induced Enteric Tumors in Germfree Rats.** (Eng) Asano, T. (Lobund Lab., Dept. Microbiology, Univ. Notre Dame, Notre Dame, IN, 46556); Pollard, M. *Proc Soc Exp Biol Med* 158(1): 89-91; 1978.

Three strains of germfree rats (Sprague-Dawley, Lobund-Wistar, and Buffalo) were tested for their susceptibility to 1,2-dimethylhydrazine (DMH)-induced enteric neoplasms. At 20 wk after the start of DMH administration (30 mg/kg po 1x/wk for 10 wk), the rats were killed and examined for tumors. Sprague-Dawley rats showed the most susceptibility to DMH carcinogenesis, Buffalo rats were intermediate, and Lobund-Wistar rats were not susceptible. The results demonstrate that intestinal microflora are not essential to the induction of intestinal tumors by DMH in Sprague-Dawley and Buffalo strain rats and that there is a strain dependent differential susceptibility to DMH-induced enteric tumors. (11 refs)

78-5495 **Transplantation of Uterine Sarcoma Induced by 1,2-Dimethylhydrazine in CBA Mice.** (Rus) Bazlova, L. S. (Lab. Carcinogenic Substances, Oncological Res. Center, Acad. Medical Sciences USSR, Moscow, USSR). *Vopr Onkol* 24(9): 80-82; 1978.

The transplantability of 1,2-dimethylhydrazine (DMH)-induced uterine sarcomas was studied in nine consecutive generations of CBA mice. The primary tumor was induced in the mice by sc administration of DMH (8 mg/kg/wk) for 30-35 wk, after which time the animals were sacrificed. In addition, the primary tumor tissue homogenate was transplanted sc into 2-mo-old female, castrated and old female, and male CBA mice. The tumor take rate was 100% in all nine generations. The latent period averaged 33-73 days in generation 1, 7-12 days in generation 3, and 4-5 days in generation 9. Survival from the date of transplantation averaged 63-108 days in generation 6, 23-38 days in generation 3, and 19-50 days in generation 9. The tumor growth dynamics were the same in young mice as in old and castrated females, and in males. The transplanted tumors retained the histol characteristics of the primary tumor. The findings in a reduction of the latent period and survival over the co tive generations. (3 refs)

78-5496 **Ultrastructure of 1,2-Dimethylhydrazi duced Adenocarcinomas in Rat Colon.** Barkla, D. H. (Dept. Anatomy, Monash Univ., Clayton toria 3168, Australia); Tutton, P. J. *J Natl Cancer Inst* 1291-1299; 1978.

The ultrastructure of 1,2-dimethylhydrazine (DM duced adenocarcinomas in the SD rat colon was exa by transmission electron microscopy and compared wit of epithelial cells in the normal colon. The ultrastruct tumor cells in the S-phase was examined using ^{3}H-thym and electron microscope autoradiography. The tumors induced in eight male SD rats by weekly sc injectio DMH (21 mg/kg) for 20 wk. Morphologically, most t cells resembled undifferentiated crypt cells of normal epithelium; a minority of tumor cells closely resembled were often indistinguishable from, differentiated colo thelial cells. Consistent abnormalities in the morpholo the basal lamina at the interface between tumor epith and adjacent lamina propria mucosae were observed. tumor cells showed ultrastructural but not light micro evidence of degeneration. Comparisons between tumo and normal epithelial cells did not reveal a single morph ic feature characteristic of the former. Autoradiograph dicated that tumor cells of widely divergent morphology capable of thymidine uptake; these tumor cells included cells and cells showing changes usually associated with n sis. S-phase tumor cells lacked distinctive ultrastructura tures in the autoradiographic studies. The ultrastruc morphology of tumor cells during the cell cycle may be studied with tumor cells in culture, because of the oppo ty to synchronize cell cycles. (29 refs)

78-5497 **1,2-Dimethylhydrazine-induced Large Cancer in Rats.** (Jpn) Miyoshi, T. (Third Surgery, Faculty Medicine, Univ. Tokyo, Bunkyo-ku, T 113, Japan); Ohhara, T.; Morioka, M. *Jpn J Gastroe* 75(3): 284-293; 1978.

1,2-Dimethylhydrazine (DMH)-induced large bowel c was studied in 40 rats autopsied 220 days after the st DMH treatment. Histologically, four types of lesions found upon serial sectioning of the entire colon: aty glands, adenoma, noninvasive cancer, and invasive ca As many as 86% of the colonic adenocarcinomas origi de novo; the remaining 14% arose from an adenoma. of the tumors occurred in the left half of the colon, and was a tendency toward tumor multiplicity. The tumor included well-differentiated adenocarcinomas, poorly

iated adenocarcinomas, and mucinous carcinomas, and was high incidence of peritoneal dissemination and ab-nal lymph node metastasis. (27 refs)

398 **Acute and Chronic Effects of 1,2-Dimethylhydrazine in Mouse Large Bowel.** (Eng) Deschner, (Memorial Sloan Kettering Cancer Center, New York, 0021); Long, F. C. *In: Prevention and Detection of Can-roceedings of the Third International Symposium on De-n and Prevention of Cancer Held by the International Group for the Detection and Prevention of Cancer in York, April 26 - May 1, 1976.* International Study Group ie Detection and Prevention of Cancer. (New York, Vol. 2(Part 1), 2404 pp.; 1319-1328; 1978.

acute and chronic effects of 1,2-dimethylhydrazine H) on the colon were studied in 90 female CF_1 mice that ed 20 mg/kg DMH sc 1x/wk for 6 wk. Acute effects evaluated in 24 mice sacrificed within the first 6 wk; ic effects were evaluated in the remaining animals, were sacrificed at 12-86 wk. Massive cell loss was seen after the first DMH injection, followed by an elevated ymidine labeling index at 48 hr and an increased mitotic ency at 72 hr. These changes were accompanied by de-ed mucus production and deformation of the crypt ure. By days 7 and 8, the histologic and autoradio-ic parameters appeared normal. Between 2 and 4 days the first injection, increased numbers of labeled cells seen in the upper third of the crypt. This labeling in the r zone appeared to occur whenever cells in the middle of the crypt were more actively involved in DNA syn-s. The loss of regulatory controls that normally repress A synthesis in the upper crypt and the increased prolifer-activity of the mid crypt were the earliest molecular ns observed in the DMH-treated colonic mucosa. Focal as were observed after three injections. Focal atypias, ps, and carcinomas developed, primarily in the distal co-in 95% of the mice sacrificed after 20 wk. The colonic ors were mainly sessile or pedunculated adenomas, ocarcinomas, and squamous cell carcinomas of the anal osa. This cancer model, involving six injections rather the previously used 26, more closely mimics the number, ibution, and developmental pattern of colonic tumors in ans. (15 refs)

499 **New Aspects of Intestinal Carcinogenesis by 1,2-Dimethylhydrazine Dihydrochloride IH) and the Influence of Antilymphocyte Globuline G) on its Progress.** (Eng) Nomura, K. (Dept. Surgery, v. Tokyo Sch. Medicine, Hongo 7-3-1, Bunkyo-ku, Tokyo Japan); Schlake, W.; Grundmann, E. *Z Krebsforsch*): 17-33; 1978.

induction of intestinal tumors by 1,2-dimethylhydrazine ydrochloride (DMH) was studied in 10-wk-old male Wistar rats that were treated with or without antilymphocyte globulin (ALG). A 1% aqueous soln of DMH was administered sc, 1x/wk over 16 wk, at a weekly dose of 20 mg/kg; total dose was about 120 mg/rat. Some rats were also given a 1-mg/0.5-ml aqueous soln of ALG ip, 2x/wk ip over 13 wk, starting 1 wk prior to DMH. During the first week, a double dose was given; total dose was 28 mg/rat. All rats had the following changes in the intestinal mucosa, regardless of treatment: glandular hyperplasia with goblet cell depletion and elongation of the germ cell zone (5-13 wk); glandular atrophy intermingled with hyperplasia (after 13 wk); neoplastic microlesions (17 wk); macroscopic tumors (21 wk). Tumor induction was negative in 5/37 rats at the last autopsy (after 33 wk). The classification of the growth pattern of macroscopic tumors corresponded to their histology. Adenomas or well-differentiated adenocarcinomas formed pedunculated tumors; moderately differentiated adenocarcinomas formed sessile tumors, often with cyst formation; and poorly differentiated or signet ring cell carcinomas formed flat tumors. Most of the tumors were located 7-25 cm from the pylorus, and they were distributed diffusely throughout the large intestine. Tumors were often accompanied by metastases, which were first seen at 29 wk. Neither tumor induction nor tumor growth were accelerated by ALG. However, metastatic dissemination and conglomerate formation occurred more frequently in the ALG + DMH group than in rats receiving only DMH. (37 refs)

78-5500 **Effect of Hydrazine, Isonicotinic Acid Hydrazide, Hydrazine Sulfate, and Dimethylhydrazine on Guanylate Cyclase Activity.** (Eng) Vesely, D. L. (Div. Endocrinology and Metabolism, Dept. Medicine, Univ. Miami Sch. Medicine, Miami, FL, 33155); Rovere, L. E.; Levey, G. S. *Enzyme* 23(5): 289-294; 1978.

Isonicotinic acid hydrazide, hydrazine sulfate, and dimethylhydrazine, three chemical carcinogens structurally related to hydrazine [a potent stimulator of guanylate cyclase (GC)], decreased GC activity. In addition, hydrazine increased DNA synthesis but the other three compounds decreased DNA synthesis. There may be a relationship between the GC-cyclic guanosine monophosphate system and DNA synthesis and chemical carcinogenesis. (41 refs)

78-5501 **The Measurement of PAHs in Industrial Effluents.** (Eng) Jones, P. W. (Battelle, Columbus Labs., Columbus, OH, 43201). *Proc Anal Div Chem Soc* 15(5): 158-159; 1978.

Methods for measuring of polycyclic aromatic hydrocarbons in industrial emissions are outlined. Macroreticular resins are used to collect samples from stack gases and aqueous effluents. Quantitative analysis is accomplished by capillary column gas chromatography-mass spectrometry utilizing selec-

tive ion monitoring. Some of the specificities for these procedures are outlined. (no refs)

78-5502 **Computer-generated Graphic Models of the N^2-substituted Deoxyguanosine Adducts of 2-Acetylaminofluorene and Benzo(a)pyrene and the O^6-substituted Deoxyguanosine Adduct of 1-Naphthylamine in the DNA Double Helix.** (Eng) Beland, F. A. (Dept. Health, Education, and Welfare, Food and Drug Admin., Natl. Center Toxicological Res., Jefferson, AR, 72079). *Chem Biol Interact* 22(2/3): 329-339; 1978.

Computer models of three deoxyguanosine-carcinogen adducts in double-helical DNA are presented. The 2-acetylaminofluorene adduct was situated in the minor groove, had little freedom of rotation, and caused little helical distortion. The anti-benzo(a)pyrenediol epoxide-N^2 adduct had a similar fit with a greater degree of steric interaction. The 1-naphthylamine derivative was in the major groove, did not perturb the helix, and had considerable freedom of movement. (31 refs)

78-5503 **Ca^2+-dependent ATPase Activity in Primary Cultures of Normal Rat Cells after Exposure to Carcinogens and Their Noncarcinogenic Analogs.** (Rus) Khodosova, I. A. (Lab. Tumor Cell Genetics, Inst. Cytology, Leningrad, USSR); Fridlianskaia, I. I. *Tsitologiia* 20(4): 470-472; 1978.

The effect of the carcinogens dimethylnitrosamine (DMNA), urethane (UT), 1,2,5,6-dibenz(a)anthracene (DBA), and 7,12-dimethylbenz(a)anthracene (DMBA) and their noncarcinogenic analogs on the activity of Ca^{2+}-dependent ATPase was studied in primary cultures of rat explant (heterogeneous population of muscle and connective tissue cells). The cell cultures were incubated with the test agents for 20 hr. Ca^{2+}-dependent ATPase activity was significantly decreased after exposure to 1,2,5,6-DBA and DMBA (to 1.44 and 1.49 IU, compared with 2.54 IU in controls and 2.75 IU in cultures exposed to the noncarcinogen 1,2,3,4-DBA). UT also inhibited the activity of the enzyme (1.95 IU), but not DMNA. (9 refs)

78-5504 **The Covalent Binding of Polycyclic Hydrocarbons to DNA in the Skin of Mice of Different Strains.** (Eng) Phillips, D. H. (Chester Beatty Res. Inst., Inst. Cancer Res., Royal Cancer Hosp., Fulham Road, London SW3 6JB, England); Grover, P. L.; Sims, P. *Int J Cancer* 22(4): 487-494; 1978.

The binding of ^{3}H-labeled 7,12-dimethylbenz(a)anthracene (DMBA), benzo(a)pyrene (BP), and 3-methylcholanthrene (3-MC) to DNA in mouse skin was studied in C5 DBA/2, and Swiss mice following topical applic C57BL mice were treated with 0.025-1 micromole (μ DMBA, and the levels of hydrocarbon bound to DNA after treatment were determined; there was no evider a threshold dose below which no binding to DNA occ From 6 hr to 8 days after treatment, DMBA was bou a similar extent in Swiss and C57BL mice and to a sl greater extent in DBA/2 mice. The rate of disappearar bound DMBA from DNA was similar in all three strain and 3-MC (each, 1 μmol) were bound to DNA to a si extent at 19 and 48 hr after treatment in all three strain (0.1 μmol) was bound to DNA in the order DBA/ C57BL/6 > Swiss 19 hr after treatment. The levels of ing did not correlate with the reported susceptibilities three strains to polycyclic hydrocarbon carcinogenesis rapid disappearance of bound DMBA from DNA sug that the modified bases are detected and excised fror DNA by repair enzymes. DNA repair in strains susce to hydrocarbon carcinogenesis may be more prone to than repair in the more resistant strains, and carcinoge may result from an alteration of the DNA sequence c by the incorrect repair of hydrocarbon-modified base refs)

78-5505 **Multiple Regions of Metabolic Activati Carcinogenic Hydrocarbons.** (Eng) Harve G. (Ben May Lab. Cancer Res., Univ. Chicago, Chicag 60637); Dunne, F. B. *Nature* 273(5663): 566-568; 197

The carcinogenicities of a series of methyl and fluoro d tives of benzo(a)pyrene (BP), 7-methylbenz(a)anthr (MBA), and 7,12-dimethylbenz(a)anthracene (DMBA) studied in male Long-Evans rats to determine wh metabolites other than bay region diol epoxides are the forms of some carcinogenic hydrocarbons. The introdu of methyl or fluoro groups into the ring of a polycyclic that was potentially capable of metabolic activation to region diol epoxide frequently, but not always, abolished cinogenic activity. Thus, 7,10-dimethy 2-methyl-DMBA, 3-methyl-DMBA, 1-fluoro-DM 2-fluoro-DMBA, and 4-methyl-MBA were inactive 10-methyl-BP was an extremely weak carcinogen, 7-methyl-BP and 4-methyl-DMBA were very potent car gens and 4-fluoro-DMBA and 2-fluoro-MBA exhibite minished but still significant carcinogenic activity. Thes sults suggest that metabolic inactivation by mixed-function oxidases occurs relatively efficiently at stituted positions or, more probably, that it can occur at native molecular regions when reaction at preferred si blocked. Although clear-cut evidence concerning the s tures of the active metabolites of any of these compoun lacking, the most probable candidates are arene oxides i substituted ring, K-region arene oxides, or non-bay re diol epoxides. (15 refs)

506 **Difference in the Induction of Osteosarcoma in Rabbit Bone with Single Administration of e Kinds of Chemical Carcinogens.** (Eng) Sato, K. (Dept. Surgery, Sch. Medicine, Chiba Univ., Inohana 1-8-1, a 280, Japan); Nukaga, H.; Horikoshi, T.; Iwasaki, I. *n* 69(4): 579-583; 1978.

osarcoma (OS) induction was evaluated in mixed breed its treated with a single intramedullary dose (15-20 mg) nitroquinoline 1-oxide (4-NQO), 3-methylcholanthrene IC), or 7,12-dimethylbenz(a)anthracene (DMBA) in the dible, diaphysis, or distal metaphysis of the femur. QO was the most effective carcinogen, with OS incidence e mandible, diaphysis, and metaphysis being 6/10, 3/10, 5/8 rabbits, respectively. In addition, there were two fi- arcomas in the diaphysis and a chondrosarcoma in the physis. Tumor incidence with DMBA was 1/10 and 2/6 its in the mandible and metaphysis, respectively; and C produced only one fibrosarcoma in a mandible. Histo- al examination of each site during the latent period re- ed that three types of tissue reaction were common, de- ling on the degree of necrotic (I), fibroblastic (II), or oid (III) tissue encountered. The development of each was related to the dose and nature of the carcinogen. e I resulted when the effectiveness or dosage of carcino- was low, and it usually appeared in sites lacking cancel- bone marrow, such as the diaphysis. Type III resulted the use of a more potent carcinogen and dose, and it lly appeared in bones containing abundant cancellous row, such as the metaphysis. Type III resulted in the ation of OS's and occasional chondrosarcomas; fibrosar- as were seldom observed. (8 refs)

5507 **Transformation of Human Cells in Culture by Chemical Carcinogens.** (Eng) Rhim, J. S. (Dept. cer Res., Microbiological Associates, Inc., Bethesda, , 20014). *In: Prevention and Detection of Cancer. Proceed- of the Third International Symposium on Detection and vention of Cancer Held by the International Study Group he Detection and Prevention of Cancer in New York, April May 1, 1976.* International Study Group for the Detec- and Prevention of Cancer. (New York, NY): Vol. 2(Part 2404 pp.; 1337-1357; 1978.

transformation of human osteosarcoma clonal cells in o with N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) ,12-dimethylbenz(a)anthracene (DMBA) was investigat- In cultures treated with MNNG (0.01 or 0.1 μg/ml), phological alterations of cells and abnormal growth pat- ns were observed in the sixth subculture. In cultures ted with DMBA (2.5 or 1.0 μg/ml), morphological rations were seen in the fifth subculture. Five/five e mice given 5 x 10^6 cells sc from cultures treated n 0.01 μg/ml MNNG developed poorly differentiated omas within 2 wk at the inoculation site. Three/five e given cells from cultures treated with 0.1 μg/ml MNNG produced small, persistent nodules resembling osteosarcomas. Three/three mice inoculated sc with 5 x 10^6 cells from cultures treated with 1.0 μg/ml DMBA developed tumors at the inoculation site within 3 wk; 0/4 animals inoculated sc with cells treated with 2.5 μg/ml DMBA developed tumors. However, cells from cultures treated with both DMBA concentrations were tumorigenic when inoculated intracranially. Human cells resembling the original, nontransformed osteosarcoma were recovered from the brain tumors, while sc tumors resembled the DMBA-treated cells. MNNG- and Kirsten sarcoma virus-transformed cells formed larger cell aggregates than did control, normal counterpart cells within 1-3 days when suspended in the liquid growth medium above an agar base. The size and degree of cell proliferation in the aggregates correlated well with tumorigenicity in nude mice. (25 refs)

78-5508 **Explant Culture of Rat Colon: A Model System for Studying Metabolism of Chemical Carcinogens.** (Eng) Autrup, H. (NCI, Bethesda, MD, 20014); Stoner, G. D.; Jackson, F.; Harris, C. C.; Shamsuddin, A. K.; Barrett, L. A.; Trump, B. F. *In Vitro* 14(10): 869-877; 1978.

An explant culture system was developed for the long-term maintenance of rat colonic tissue. Colonic explants (1 cm^2) from male Charles River CD rats (4-5 wk old) or adult male Fisher F-344 rats were placed in tissue culture dishes with the epithelium facing the gas-medium interface. Two milliliters of CMRL-1066 culture medium supplemented with glucose, hydrocortisone, β-retinyl acetate, and either 2.5% bovine albumin or 5% fetal bovine serum were added to each dish. The explants were incubated at 30 C in an atmosphere of 95% O_2 and 5% CO_2 on a rocker platform (10 cycles/min) so that the explant was submerged half the time. Under these conditions, the normal appearance of the colonic epithelium was maintained for at least 63 days. After 4 days in culture, one of the following carcinogens was added to the medium to investigate the ability of the explant to metabolize carcinogens: benzo(a)pyrene (BP: 1.5 μM), 7,12-dimethylbenz(a)anthracene (DMBA: 3.2 μM), aflatoxin B_1 (AFB_1: 0.5 μM), 1,2-dimethylhydrazine (1,2-DMH: 1.3 mM), methylazoxymethanol acetate (MAM: 0.26 mM), and dimethylnitrosamine (DMN: 135 μM). After 24 hr incubation (8 hr for MAM), the highest binding level was observed with 1,2-DMH [13,526 picomoles (pmol) carcinogen bound/10 mg DNA]. The other carcinogens bound in the following order: DMH (5,000 pmol/10 mg), MAM (1,650), DMN (845), AFB_1 (125), DMBA (5.2), and BP (3.5). Thus, cultured rat colon was able to metabolize all carcinogens tested into chemical species that formed covalent bonds with cellular DNA. (27 refs)

78-5509 **Stimulation by Carcinogens and Promoters of Prostaglandin Production by Dog Kidney (MDCK) Cells in Culture.** (Eng) Levine, L. (Graduate Dept Biochemistry, Brandeis Univ., Waltham, MA, 02154); Ohu-

chi, K. *Cancer Res* 38(11, part 2): 4142-4146; 1978.

The effect of carcinogens and tumor promoters on prostaglandin (PG) production was studied in dog kidney cells (MDCK) in culture. The most active polycyclic aromatic hydrocarbon carcinogens, benzo(a)pyrene (BP), 7,12-dimethylbenz(a)anthracene, and 3-methylcholanthrene (each, 0.5 μg/ml), stimulated PG production and the deacylation of cellular lipids, as did aflatoxin B_1 at 0.05 and 0.02 μg/ml. Neither the aromatic amines nor the nitrosamines, at 0.5 μg/ml, affected PG production. Purified epidermal growth factor (EGF: 10^{-9} to 10^{-10} M) also stimulated PG production and cellular lipid deacylation. 12-Tetradecanoylphorbol-13-acetate (TPA) and phorbol-12,13-didecanoate (PDD),each 10^{-9} to 10^{-10} M, stimulated PG synthesis, the deacylation of cellular lipids, and morphological changes in the MDCK cells. The increased PG synthesis and morphological changes required at least 24 hr for expression. Cycloheximide inhibited the TPA- and PDD-stimulated changes but hydrocortisone did not. The PG synthesis stimulated by TPA and PDD was reversible. In terms of the two-stage model of skin carcinogenesis, some of the carcinogens, EGF, TPA, and PDD may be acting as promoters. The mechanism of action of the biologically active phorbol diesters (and that of all promoters) may be related to their antidifferentiation properties. It is possible that deacylation of cellular lipids and/or arachidonic acid metabolism via the cyclooxygenase system mediates cellular differentiation. (27 refs)

78-5510 **Association and Dissociation of the Ah Locus with the Metabolism of Aflatoxin B_1 by Mouse Liver: Co-segregation of Aflatoxin B_1 Hydroxylase Induction with Aryl Hydrocarbon (Benzo(a)pyrene) Hydroxylase Induction.** (Eng) Gurtoo, H. L. (Dept. Experimental Therapeutics, Grace Cancer Drug Center, Roswell Park Memorial Inst., Buffalo, NY, 14263); Dahms, R. P.; Kanter, P.; Vaught, J. B. *J Biol Chem* 253(11): 3952-3961; 1978.

The hepatic microsomal NADPH-mediated metabolism of aflatoxin B_1 (AFB) and its response to induction by phenobarbital (PB) and/or 3-methylcholanthrene (3-MC) were studied in 70 mice representing various inbred strains, recombinant inbred lines, and progenies of various crosses. The metabolism of AFB to alfatoxin B_1-2,3-oxide and to aflatoxin M_1 (AFM) was preferentially catalyzed by cytochrome P-450- and cytochrome P_1-450-dependent pathways, respectively. AFB epoxidation, which was induced by PB in mice of various inbred strains or recombinant inbred lines, was not associated with the Ah locus. 3-MC pretreatment depressed the epoxidation of AFB 10%-70% in all the strains and recombinant inbred lines tested. This pretreatment induced AFB hydroxylase activity, leading to the formation of AFM, in only some inbred strains. The strains of mice inducible for AFB hydroxylase (8/17 strains tested) were also inducible for aryl hydrocarbon hydroxylase (AHH). The induction of AFB hydroxlyase and AHH by 3-MC was also examined in various hybrid and backcross progenies and in several rec nant inbred lines. The results suggest that the inducti AFB hydroxylase is regulated by a single gene locus wit alleles, one of which is dominant over the other. The r also suggest that the regulation of the induction of AF droxylase and its association with the induction of AH cur at the level of common regulatory factors and tha same genetic factors regulate the induction of micros and nuclear AFB hydroxylase activities. (72 refs)

78-5511 **Induction of Sister-Chromatid Exchang Chinese Hamster Ovary Cells Treated In with Non-K-Region Dihydrodiols of 7-Methylbenz(a)a cene and Benzo(a)pyrene.** (Eng) Pal, K. (Chester Beatty Inst., Inst. Cancer Res., Royal Cancer Hosp., Fulham London SW3 6JB, England); Tierney, B.; Grover, P. L.; P. *Mutat Res* 50(3): 367-375; 1978.

Benzo(a)pyrene (BP) and 7-methylbenz(a)anthr (MBA) and a series of related K-region and non-K-r diols were tested for their abilities to induce sister chro exchanges (SCE's) in Chinese hamster ovary (CHO) c vitro. BP and the related 4,5- and 9,10-dihydrodiols weakly active in inducing SCE's, the hydrocarbon somewhat more cytotoxic than either of the diols. Hov the 7,8-dihydrodiol was much more active than the compounds, and it was highly cytotoxic. The 3,4-dihyd of MBA was cytotoxic to CHO cell cultures at high co trations and was considerably more active in inducing than the parent compound or the 1,2-, 5,6-, or 8,9-dihy ols. The compounds in the MBA series induced more per metaphase plate than those in the BP series. The r suggest that this system may be useful in studies aim determining which dihydrodiols are important in the bolic activation of the carcinogenic polycyclic hydroca It is concluded that CHO cells possess some intrinsic to metabolize such compounds in the absence of exog activation systems. (39 refs)

78-5512 **Molecular Orbital Theoretical Prediction Isomeric Products Formed from Reactio Arene Oxides and Related Metabolites of Polycyclic matic Hydrocarbons.** (Eng) Fu, P. P. (Ben May Lab., Chicago, Chicago, IL, 60637); Harvey, R. G.; Beland, *Tetrahedron* 34(7): 857-866; 1978.

The simplified perturbational molecular orbital theory war was used to predict the isomeric reaction produ arene oxides and related metabolites of polycyclic aro hydrocarbons (PAH). This technique provided a good lation between the predicted and observed structures o ducts formed during the isomerization of arene oxides t nols, the hydration and nucleophilic addition to arene o and the dehydration of arene dihydrodiols. The metho also applicable to the arene oxides and dihydrodiols d

carcinogenic and noncarcinogenic PAH. Extension of findings to the enzymatic reactions occurring during metabolism of carcinogenic hydrocarbons and to the reac- of the biologically active arene diolepoxides and aryloxi- suggests that this method may be useful in predicting metabolite structure and structural requirements for car- genic and mutagenic activity. (39 refs)

513 **Effect of Light on the Hydrocarbon-DNA Adducts Formed in Hamster Embryo Cells.** (Eng) d, W. M. (Wistar Inst. Anatomy and Biology, 36th St. pruce, Philadelphia, PA, 19104). *Int J Cancer* 22(3): 297; 1978.

an hamster embryo cells in culture were used as a model em to determine how exposure to light (fluorescent light, affects the formation and structure of the DNA adducts ,12-dimethylbenz(a)anthracene (DMBA, highly photo- itive) and benzo(a)pyrene (BP, less photosensitive). Cells e exposed to FL (Group A) or kept in darkness (Group uring a 48-hr incubation with 0.5 μM of hydrocarbon. DNA of the Group B cells was exposed to FL before fter enzymatic digestion to deoxyribonucleosides. In cells ted with DMBA, the total amount of DMBA-DNA ad- s formed per milligram of DNA was less in Group A cells in Group B cells. No appreciable amounts of hydrocar- DNA adducts were formed in Groups A and B cells ed with DMBA endoperoxide, a major photooxidation uct of DMBA. The DMBA-deoxyribonucleoside ad- s obtained from Group B cells were analyzed by chroma- aphy on Sephadex LH20 columns. Exposure of these ad- s to FL converted more than half to photoproducts. A that was exposed to FL prior to degradation contained than half as many photoproducts and had an elution ile similar to that obtained from DNA isolated from up A cells. The BP-DNA adducts were identical for the A from Groups A and B cells and for the DNA exposed L after isolation. These results indicate that exposure to does not alter the mechanism of binding of hydrocar- to DNA in hamster embryo cells but that it does affect DNA adducts of DMBA in a similar manner in cells and olated DNA. The biological effects of the light-induced ification of DMBA-DNA adducts in cells are not known. possible that degradation-resistant DMBA cross-links formed in the DNA, a phenomenon that would greatly ease the biological consequences of the interaction of this rocarbon with DNA. (31 refs)

5514 **Comparative Mutagenesis of Test Materials from the Synthetic Fuel Technologies (Meeting stract).** (Eng) Epler, J. L. (Biology Div., Oak Ridge Natl. ., Oak Ridge, TN, 37830); Larimer, F. W.; Nix, C. E.; T.; Rao, T. K. *Mutat Res* 53(2): 185; 1978. (no refs)

78-5515 **Testing of Carcinogens and Chemotherapeutic Agents as Inducers of Bacteriophage Lambda (Meeting Abstract).** (Eng) Elespuru, R. K. (Molecular Genetics Section, Frederick Cancer Res. Center, Frederick, MD, 21501); Yarmolinsky, M. B. *Mutat Res* 53(2): 184-185; 1978. (1 ref)

78-5516 **A Biological Analysis of Chemical Hepatocarcinogenesis. (Meeting Abstract).** (Eng) Solt, D. B. (Temple Univ., Philadelphia, PA, 19122). *Diss Abstr Int B* 39(4): 1711; 1978. (no refs)

78-5517 **Induction of the Metabolic Activation System in Rat Liver by a Combined Treatment with 5,6-Benzoflavone and Phenobarbital; Comparison with Aroclor 1254, Using the Ames Test (Meeting Abstract).** (Eng) Mattern, I. E. (Medical Biological Lab. TNO, P.O. Box 45, Rijswijk, Netherlands). *Mutat Res* 53(2): 227-228; 1978. (1 ref)

78-5518 **Mutability of Different Genetic Loci in Mammalian Cells by Metabolically Activated Chemical Carcinogens (Meeting Abstract).** (Eng) Huberman, E. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN). *Mutat Res* 53(2): 202-203; 1978. (no refs)

78-5519 **Comparative Survey of Microsomal Activation Systems for Mutagenic Studies of Safrole (Meeting Abstract).** (Eng) Dorange, J. L. (Station de Technologie des Produits Vegetaux, 21034 Dijon, France); Janiaud, P.; Delaforge, M.; Levi, P.; Padieu, P. *Mutat Res* 53(2): 179-180; 1978. (6 refs)

78-5520 **Inhibition of Chemical Carcinogenesis by *Corynebacterium parvum*.** (Eng) Woodruff, M. (MRC Clinical and Population Cytogenetics Unit, Western General Hosp., Crewe Road, Edinburgh, EH4 2XU, Scotland); Speedy, G. *Proc R Soc Lond [Biol]* 201(1143): 209-215; 1978.

The development of fibrosarcomas in female CBA mice inoculated im with 20-methylcholanthrene (20-MC: 0.5 mg in 0.1 ml tricaprylin) was inhibited significantly by *Corynebacterium parvum* (0.7 mg) administered iv 4 days before the carcinogen and then every 28 days. Similar treatment starting 4 wk after 20-MC injection did not alter the tumor incidence. Based on these results and previous studies of the effect of *C. parvum* on macrophage activity, it is postulated that a transformation event occurring shortly after 20-MC exposure

results in the emergence of a cell population that is liable to destruction by activated macrophages. However, if the cells are not destroyed, they may multiply so rapidly that subsequent treatment is unable to prevent or delay tumor appearance. (27 refs)

78-5521 **Induction of Neoplasms in Hamster Tracheal Grafts with 3-Methylcholanthrene-coated Lycra Fibers.** (Eng) Mossman, B. T. (Dept. Pathology, Univ. Vermont Coll. Medicine, Burlington, VT, 05401); Craighead, J. E. *Cancer Res* 38(11, part 1): 3717-3722; 1978.

A method was devised to improve the quantitation of carcinogen dosage to the tracheal epithelium of hamsters. Synthetic Lycra spandex fibers were immersed in 0.3-30 mg/ml solns of ^{14}C-labeled or unlabeled 3-methylcholanthrene (3-MC) for 1 wk and then inserted into the lumina of 104 tracheas removed from young adult Syrian hamsters. Tracheas were grafted sc onto the backs of 22 weanling hamsters (each animal received 3-4 grafts), and the animals were examined at 3-wk intervals for tumors. Tumors appeared in the tracheal epithelium 3-21 mo after implantation, and they included small cell carcinomas, squamous cell carcinomas, noninvasive carcinomas, papillomas, fibrosarcomas, and adenocarcinomas. Most were carcinomas. The neoplasms were induced with 3-MC doses up to 100-fold lower (9-75 μg/fiber) than amounts used by other investigators. The use of tracer quantities of ^{14}C-3-MC allowed quantitation of the dose to the tracheal mucosa before and at intervals after grafting. A dose-dependent sensitivity of the hamster tracheal epithelium to relatively small quantities of 3MC was demonstrated. (18 refs)

78-5522 **Sequential Cytologic Study of the Development of Squamous Cell Carcinoma Induced in Subcutaneously Implanted Bronchial Autograft of Dog.** (Eng) Kobayashi, N. (Inst. Pulmonary Cancer Res., Sch. Medicine, Chiba Univ., Chiba, Japan); Kanisawa, M.; Okamoto, T.; Okita, M.; Katsuki, H. *Acta Cytol (Baltimore)* 22(2): 99-104; 1978.

The lumina of canine bronchi implanted in sc tissue were exposed to the carcinogens 3-methylcholanthrene or benzo(a)pyrene (30-90 mg in a saline soln containing 1% carboxymethylcellulose). The exfoliative cytology and the corresponding histologic and ultrastructural changes during the development of squamous cell metaplasia and carcinoma in the autografts were followed in needle biopsy specimens obtained at intervals of 4-22 wk. The cytologic specimens showed a progression from mild atypia of squamous metaplastic cells to moderate and marked atypia before the development of invasive squamous cell carcinoma. The histologic findings corresponded to these cytologic changes. In the premalignant phase, squamous dysplasia and changes resembling carcinoma in situ were also seen. Ultrastructural changes in the preneoplastic stages included widened cellular space, increasing tonofilaments, enlarged nucle deep indentations, and prominent nucleoli with micro gation. It is concluded that exfoliative cytology, refl histologic and ultrastructural changes, is a useful tool f comparative study of premalignant lesions in the h bronchus and their early neoplastic stages. (21 refs)

78-5523 **Carcinogenicity and Metabolic Profil 3-Methylcholanthrene Oxygenated Deriv at the 1 and 2 Positions.** (Eng) Cavalieri, E. (Eppley Ins Cancer, Univ. Nebraska Medical Center, 42nd and I Ave., Omaha, NB, 68105); Roth, R.; Althoff, J.; Gran C.; Patil, K.; Marsh, S.; McLaughlin, D. *Chem Biol In* 22(1): 69-81; 1978.

To support the hypothesis that the critical mechanism c vation of 3-methylcholanthrene (3-MC) is one-electro dation, its carcinogenicity was compared with th 1-hydroxy-3-methylcholanthrene (MC-1-OH), 3-m cholanthrene-1-one (MC-1-one), 2-hydroxy-3-m cholanthrene (MC-2-OH), 3-methylcholanthrene (MC-2-one), and 3-methylcholanthrylene (MCL) by re application on mouse skin. Six groups of 30 7-wk-old f Swiss mice were treated with 0.2 micromole of compo acetone 2x/wk for 20 wk. All mice tested with MC-2-OH, and MC-2-one developed skin neoplasms, b latter two groups showed later tumor development and er survival. MCL and MC-1-OH showed a weake cinogenicity, and MC-1-one was not carcinogenic. MCL group, the percentage of epidermal carcinom metastases to the lungs was more than twice that of the groups. The results support the hypothesis that one-el oxidation for 3-MC, MC-2-OH, and MC-1-one might critical mechanism of carcinogenic activation, with C binding site to cellular nucleophiles. The carcinogenic of MC-1-OH could be due to the formation of an este might be the ultimate intermediate in the reaction with lar nucleophiles. Finally, the lack of carcinogenici MC-1-one may be due to absence of nucleophilic trapp C-1 via the radical cation pathways as well as to the in of mouse skin to reduce MC-1-one to MC-1-OH. The of metabolism studies of the compounds using mous homogenates are also reported. (20 refs)

78-5524 **Cyclophosphamide Delays 3-Methylcho rene Sarcoma Induction in Mice.** (Eng) strom, I. (Div. Immunology, Fred Hutchinson Cance Center, Seattle, WA, 98104); Hellstrom, K. E. 275(5676): 129-130; 1978.

The hypothesis that treatment of mice with cyclophe mide (CP) during the latency period of tumor ind might prevent or at least delay the appearance of pr tumors was investigated. BALB/c mice were divided in

ps, all of which were inoculated im with 0.1 mg thylcholanthrene (3-MC) on day 1. On days 10, 20, 50, 80, Groups 1 and 4 were inoculated with 10^6 heavily iated cells from an 3-MC-induced BALB/c sarcoma, ips 2 and 5 were inoculated with normal BALB/c kidney and Groups 3 and 6 received phosphate-buffered saline. 100 mg/kg) was injected ip into Groups 4, 5, and 6 at ay intervals starting on day -13 and continuing throughthe experiment. Groups 4, 5, and 6 developed tumors h more slowly than Groups 1, 2, and 3 (controls). At day all but one of the control mice had at least one tumor, 40% of the CP-treated mice remained tumor-free. How-, the major effect of CP was probably a delay of tumor arance rather than a prevention of tumor induction, e the appearance of new tumors in the drug-treated group not leveled off at the time of writing (142 days). The delay mor appearance is consistent with the hypothesis that inhibits tumor growth by interfering with either a supsor cell mechanism or an immunostimulatory mechm. However, it is equally consistent with the nonimological interpretations that CP destroys neoplastic cells ey develop or it interferes with carcinogenesis. (14 refs)

5525 **Effects of Essential Amino Acid Deficiencies on Syngeneic Tumor Immunity and Carcinogenesis lice.** (Eng) Worthington, B. S. (Sch. Nutritional Sciences Textiles, Univ. Washington, Seattle, WA, 98195); Syro-, J. A.; Ahmed, S. I. *J Nutr* 108(9): 1402-1411; 1978.

long-term effect of essential amino acid (AA) deficiencies nethylcholanthrene (MC)-induced carcinogenesis and on unity to a transplanted MC-induced tumor was studied bred female Balb/c AN mice. Mice were fed a standard diet or one containing 25% of the requirement of isoleu- (Ile), leucine (Leu) or phenylalanine-tyrosine (Phe-Tyr) up to 54 wk. Tumors were induced by implanting paraffin s containing 5% MC sc. In the Phe-Tyr-deficient groups, or incidence was significantly greater than that in con-; Ile or Leu deficiency had no significant effect on inci-ce. There was generally a deficit in the specific serum-free corresponding to the dietary restriction. However, tu-s from experimental and control mice were similar in AA position. Mice in the immunity study were inoculated 1 5 x 10^5 tumor cells/mouse; all tumors were excised when largest tumor in the controls reached 12 mm, 3 days later h animal was challenged with 5 x 10^5 tumor cells sc. In onse to the first inoculation, the Ile-deficient group had er (20%) and smaller tumors but the Leu-deficient group more (40%) and larger tumors than controls (32.5%). ver animals in the Phe-Tyr-deficient group had tumors %), but they were of the same size as those in controls. ere were no significant differences between the controls AA-deficient groups in response to tumor challenge. The y wt of experimental and control mice did not differ rkedly except for the Ile-deficient group, in which there s pronounced wt loss and debilitation. It is concluded that selected AA acid restriction was of no therapeutic value and appeared detrimental in the case of Phe-Tyr deficiency. (21 refs)

78-5526 **Regenerative Proliferation of Mouse Epidermal Cells Following Application of a Carcinogenic Skin Irritant (MCA): Micro-flow Fluorometric DNA Measurements and ^{3}-TdR Incorporation Studies of Isolated Basal Cells.** (Eng) Clausen, O. P. (Inst. Pathology, Univ. Oslo, Rikshospitalet, Oslo 1, Norway). *Virchows Arch Cell Pathol* 27(3): 205-215; 1978.

Changes in the cell-cycle traverse of basal cells in hairless mouse epidermis were studied after a single application of 20-methylcholanthrene (20-MC: 0.025 ml of a 1% soln in benzene). At different time intervals up to 3 days after 20-MC administration, groups of animals were injected ip with 30 μCi ^{3}H-thymidine (^{3}H-TdR) 30 min before they were killed. Single cell suspensions of epidermal basal cells were prepared, and changes in the labeling index, mean counts, and DNA distribution patterns in each cell suspension were studied in microflow fluorometry. After a slight initial depression at 6 hr after 20-MC application, the labeling index reached a peak at 16 hr, followed by a trough from 24 to 36 hr and then a second peak at 40 hr. The mean grain count was below control level at all times, except at 40 hr. Of the cells entering mitosis from 36 to 44 hr after 20-MC treatment, 65%-70% were labeled with ^{3}H-TdR. The proportion of cells with S-phase DNA content increased gradually starting at 6 hr after 20-MC application, reaching 250% of control values at 16 hr and staying at this level until 40 hr. After a slight transient increase at 6 hr, the proportion of cells with G_2-phase DNA content decreased to below control values until 40 hr, when there was an increase. From 40 to 72 hr, however, the proportion decreased again. These data indicate that there is a marked prolongation of DNA synthesis despite a consistently increased labeling index. They support the theory that a specific injury to DNA is an initial event in the carcinogen-target cell interaction. (29 refs)

78-5527 **Aprotinin and Sarcoma Induction by Methylcholanthrene in Rats.** (Ita) Laurentaci, G. (Cattedra di Chirurgia Plastica e Ricostruttiva, Universita degli Studi di Bari, Bari, Italy); Dioguardi, D.; Pascone, M. *Arch Sci Med (Torino)* 134(3): 275-281; 1978.

The effect of the immunosuppressive agent aprotinin (Trasylol) on the sarcoma-inducing effect of methylcholanthrene was studied in male and female Wistar rats. Ten rats were injected with 0.3 mg% methylcholanthrene (MC) into the proximal segment of one hindlimb (controls). Ten other rats also received injections of aprotinin (20,000 kallikrein-inhibiting units/kg/day) for 2 wk starting on the day of MC injection, at the same site. The latent period of tumor induction

was 103-157 days in the controls, and their survival after tumor appearance was 34-65 days. The latent period was 103-141 days in the aprotinin-treated group, and the survival time was 37-56 days. The findings indicate that there were no significant differences between the two groups; ie, immunosuppression failed to facilitate the growth of MC-induced sarcomas. (27 refs)

78-5528 **Studies of Experimental Lung Tumors Induced by Chemical Carcinogens and Inorganic Substances. III. Histopathological Studies of Lung Tumors Induced in Rats by Pertracheal Infusion of 20-Methylcholanthrene Combined with Chromium and Nickel Powder.** (Eng) Mukubo, K. (Second Dept. Internal Medicine, Nara Medical Univ., Nara, Japan). *J Nara Med Assoc* 29(1): 321-340; 1978.

Female rats were given a single pertracheal infusion of 20-methylcholanthrene (3-MC: 1 or 5 mg) and/or powdered chromium (10 mg) or powdered nickel (10 mg) via a vinyl tube, and histopathological studies were made 1-12 hr later. The earliest change noted was hyperplasia of the bronchioalveolar epithelium, followed by squamous metaplasia and atypical proliferation of the bronchiolar epithelium (APBE). At either dose of 3-MC, the incidence of APBE was significantly higher in the 3-MC + CR and 3-MC + NI groups than in the 3-MC alone groups. Cornifying squamous cell carcinoma developed in rats of several groups as early as 12 wk after infusion of 3-MC. The carcinoma incidence was 7/12 rats in the 3-MC (5 mg) + Cr group, 3/5 in the 3-MC (5 mg) + Ni group, 3/7 in the 3-MC (5 mg) group, 3/12 in the 3-MC (1 mg) + Cr group, 2/7 in the 3-MC (1 mg) + Ni group, and 1/8 in the 3-MC (1 mg) group. None of the tumors metastasized. In all 3-MC groups, early alveolitis reached max severity 1 wk after infusion and then subsided in subsequent weeks. This inflammatory change and the later fibrosing reactions were more apparent in the groups given 3-MC and metallic powder than in those given 3-MC alone. The results indicate that the action of 3-MC and Cr or Ni was synergistic with respect to the production of lung cancer, as APBE, which is considered a precancerous lesion, was promoted by adding the powdered metals to 3-MC. The only change noted in the Cr and Ni alone groups was hyperplasia of the bronchiolar epithelium in 3/12 and 3/7 rats, respectively. (53 refs)

78-5529 **Development of Malignant Tumors after Transplantation of Organ Lung Cultures Treated with 20-Methylcholanthrene.** (Bul) Vlasov, V. (Dept. Pathoanatomy, Medical-Biological Inst., Sofia, Bulgaria); Uzunov, P. *Onkologiia* 15(1): 25-29; 1978.

Lung explants derived from 630 A/Sn and BALB/cY mice (1-3 mo old) were cultured in medium 199, treated with 20-methylcholanthrene (4 mg/ml, for 7 days), and then transplanted sc into 126 mice. Of 87 surviving mice, 41 animals developed 44 malignant tumors from 3 to 12 mo transplantation. Most of the tumors developed after 4-7 Histologically, there were 11 carcinomas, 9 carcinosarco and 24 sarcomas. (9 refs)

78-5530 **The Formation of Dihydrodiols by Chemic Enzymic Oxidation of 3-Methylcholanth** (Eng) Tierney, B. (Chester Beatty Res. Inst., Inst. C Res., Royal Cancer Hosp., Fulham Road, London SW3 England); Hewer, A.; Rattle, H.; Grover, P. L.; Sim *Chem Biol Interact* 23(1): 121-135; 1978.

The dihydrodiol metabolites of 3-methylcholanthrene (were prepared by direct oxidation of the hydrocarbon ascorbic acid-ferrous sulfate-EDTA. All six structurally sible dihydrodiols were obtained and identified cis -2a,3- dihydroxy -3- methylcholanthrene (A), t 4,5-dihydro -4,5- dihydroxy-3-methylcholanthrene trans-7,8-dihydro -7,8- dihydroxy-3-methylcholanth (C), trans -9,10-dihydro-9,10-dihydroxy-3-methylch threne (D), cis-11,12-dihydro -11,12- dihydro methylcholanthrene (E), and trans-11,12-dihydro-1 dihydroxy-3-methylcholanthrene (F). Examinatio high-pressure liquid chromatography of the dih diols formed during the metabolism of MC by rat microsomal preparations showed the presence of D, and F. Cis- and trans-1,2-dihydroxy -3- me cholanthrene, A, and E were tentatively identifie metabolites. Microsomal preparations from the of rats pretreated with 5 mg MC (ip, 48 hr before kil formed larger amounts of dihydrodiols from ^{3}H-labeled than did preparations from untreated rats, with the excep of metabolite A. The metabolism of MC by mouse skin m tained in short-term organ culture yielded only D, toge with cis- and trans-1,2-dihydroxy-3-methylcholanthrene refs)

78-5531 **Nature of Oncofetal Antigen Expressed on thylcholanthrene-induced Sarcoma Cells Rats.** (Jpn) Takami, T. (Dept. Pathology, Sapporo Me Coll., Sapporo-shi, Hokkaido 060, Japan). *Sapporo I Zasshi* 47(4): 409-420; 1978.

The immunogenicity of oncofetal antigen(s), which ar pressed on the surface of methylcholanthrene (MC)-ind sarcoma cells, was investigated with the use of antiem sera (AES) cross-reactive between tumor and fetal cells. sera were obtained by immunizing rats with syngeneic cells in midgestation. Immunofluorescence studies and c plement-dependent cytotoxicity tests revealed that reacted with MC-induced tumor cells (KMT-17, KMT and 16 fetal cells, but it did not react with day 10 fetal and normal adult thymus cells. In absorption test, KM and KMT-50 cells had the same absorptive capability ag AES. Multiparous sera (MPS) reacted with tumor cells, their reactivity tended to increase according to the nu

gnancies. Absorption activity against MPS was high ay 16 fetuses and weak with day 13 and 14 fetuses. No y was seen with day 14 or 16 placenta. Normal sera lt rats were cytotoxic against syngeneic tumor cells, but sitive finding was obtained by indirect immuno- scence using FITC-conjugated anti-IgG serum. tion of tumor transplantation resistance failed in nmunized with syngeneic fetal cells. The results m that oncofetal antigen(s) is expressed in most cally induced tumors and that immunization with neic fetal cells can induce a humoral antibody that reacts with tumors and fetus, but no strong tumor nce such as tumor rejection is induced. (64 refs)

32 **Effect of Oil-attached BCG Cell-Wall Skeleton and Thymectomy on the Incidence of Lung Can- d Amyloidosis Induced by Chemical Carcinogens in ts.** (Eng) Hirao, F. (Third Dept. Internal Medicine, Univ. Medical School, Fukushima 1-1-50, Fuku- -ku, Osaka 553, Japan); Nishikawa, H.; Yasaki, S.; , T.; Azuma, I.; Taniyama, T.; Yoshimoto, T.; Ki- to, S.; Yamamura, Y. *Gann* 69(4): 453-459; 1978.

vestigation was made of the effect of oil-attached BCG ll skeletons (BCG-CSW) and of thymectomy on cally induced lung cancer and amyloidosis in rabbits. ts were given a mixture of 3-methylcholanthrene (40 4-nitroquinoline 1-oxide (0.4 mg) intrabronchially ev- -40 days. BCG-CWS was administered either once, in e iv injection of 5 mg, or continuously, 5 mg the first nd then 2 mg every 30-40 days. Lung cancer developed 36 rabbits treated with carcinogens alone (controls), cancer was seen in animals treated with multiple doses G-CWS. Rabbits given the single dose of BCG-CWS cancer incidence (50%) similar to that of con- 47%). Rabbits thymectomized at 30 days and subse- y treated with the carcinogen mixture had a high lung rate (32/40). There were no differences in the appear- f amyloidosis among thymectomized, BCG-CSW, and l rabbits. (17 refs)

33 **Particulate Enhanced Membrane Uptake of 1,2-Benzanthracene Observed by Fluorescence roscopy.** (Eng) Lakowicz, J. R. (Freshwater Biological Dept. Biochemistry, Univ. Minnesota, P. O. Box 100, re, MN, 55392); Englund, F.; Hidmark, A. *Biochim ys Acta* 543(2): 202-216; 1978.

transfer of 1,2-benzanthracene (BA) from the adsorbed state to phospholipid vesicles of dipalmit- -α-phosphatidylcholine was studied and compared with tes of transfer from crystalline and microcrystalline us dispersions. The fluorescence spectral shifts that oc- d upon transfer of BA from the silica surface to the holipid vesicles were used to quantitate the membrane uptake of BA from particulates. The rate of BA uptake by the dipalmitoyl-L-α-phosphatidylcholine vesicles was independent of the lipid concentration, suggesting that the solubilization rate of BA in the aqueous phase was rate limiting. The rate of membrane uptake was also independent of the surface density of BA on silica, indicating that the BA molecules were uniformly dispersed on the silica surface. Adsorption of BA to silica greatly enhanced its rate of transport into the vesicles, the silica-adsorbed BA being more rapidly transported into the vesicles than was microcrystalline BA at temperatures from 8 C to 42 C. Silica apparently did not disrupt the vesicles under the conditions used. The data indicate that particulates can act as cocarcinogens by enhancing the cellular uptake of carcinogens and by facilitating the expression of preneoplastic transformation. (27 refs)

78-5534 **Cyclic Nucleotide Concentrations in 7,12-Dimethylbenz(a)anthracene-induced Pancreatic Cancer in Rats.** (Eng) Stevens, R. H. (Radiation Res. Lab., Dept. Radiology, Univ. Iowa, Iowa City, IA, 52242); Graves, J. M.; Meek, E. S.; Osborne, J. W.; Cheng, H. F.; Loven, D. P. *J Natl Cancer Inst* 61(5): 1281-1284; 1978.

Cyclic AMP (cAMP) and GMP (cGMP) levels were measured in pancreatic adenocarcinomas induced in noninbred male Holtzmann rats by the implantation of beeswax containing 7,12-dimethylbenz(a)anthracene (DMBA) into the head of the pancreas. Within 4-6 mo after implantation, $>80\%$ of the rats developed pancreatic tumors. The cells measured for intracellular concentrations of cAMP and cGMP belonged to two distinct categories: (1) tumors and adjacent tissue that contained significantly lower amounts of the cyclic nucleotides than normal tissue; and (2) tumors and adjacent tissue that contained significantly greater amounts. The cyclic nucleotide levels detected in adjacent tissue, which appeared to be noncancerous, may reflect the presence of some neoplastic cells or may be due to effects of DMBA or its metabolites. A significantly greater cAMP/cGMP ratio was calculated for the two tumor groups, whereas no difference was found for the tissue adjacent to the tumor. These results suggest the existence of two types of tumor cells that may be under similar cyclic nucleotide control. The roles of cAMP and cGMP in the growth and differentiation of pancreatic cancer remain to be determined. (32 refs)

78-5535 **Expression of RNA of an Endogenous Replication-defective Retrovirus in Rat Mammary Adenocarcinomas Induced by 7,12-Dimethylbenz(a)anthracene.** (Eng) Young, H. A. (Lab. Tumor Virus Genetics, Div. Cancer Cause and Prevention, NCI, Bethesda, MD, 20014); Wenk, M. L.; Goodman, D. G.; Scolnick, E. M. *J Natl Cancer Inst* 61(5): 1329-1337; 1978.

The possible relationship between chemical carcinogen induction of rat mammary tumors and the expression of an

endogenous retroviral genome was investigated in female SD rats. At 50 days of age, the rats received a single 1.0-ml intragastric dose of a 20-mg/ml soln of 7,12-dimethylbenz-(a)anthracene (DMBA). At various times, tumor-bearing rats were killed and the tumor type was identified histologically. A total of 50 tumors was obtained from 17 DMBA-treated rats. Thirty-five were mammary adenocarcinomas, 5 fibroadenomas, and the remaining 10 miscellaneous lesions. The mammary adenocarcinomas were analyzed for the RNA of a replication-defective (RD) endogenous retrovirus or the RNA of a helper-independent endogenous C-type virus. Expression of RD virus RNA was detected in mammary tumors weighing 0.2-2.0 g. Larger tumors, for which histologic examination revealed proportionally more fibroblastic tissue than epithelial cells, did not contain comparable concentrations of this viral RNA. RNA homologous to a helper-independent rat C-type retrovirus was not detected in tumors of any size. A cell line was established from a primary DMBA-induced mammary adenocarcinoma and it appeared similar to the small mammary tumors with respect to endogenous C-type viral RNA expression. The results indicate the necessity of considering the role of RD endogenous retroviruses in carcinogen-induced, radiation-induced, or naturally occurring tumors in which viral particles have not been detected. (51 refs)

78-5536 **Reaction of 7,12-Dimethylbenz(a)anthracene with DNA of Fetal and Maternal Rat Tissues In Vivo.** (Eng) Doerjer, G. (Abteilung Neuropathologie, Pathologisches Institut der Universitat Freiburg, 7800 Freiburg, W. Germany); Diessner, H.; Bucheler, J.; Kleihues, P. *Int J Cancer* 22(3): 288-291; 1978.

The binding of 7,12-dimethylbenz(a)anthracene (DMBA) to DNA of various maternal and fetal rat tissues was investigated following a single injection of ^{3}H-DMBA (15 mg/kg, 48 mCi/kg, iv) to two pregnant BD-IX rats on day 21 of gestation. This dose is known to induce a high incidence of nervous system tumors in the offspring. The rats were sacrificed 12 hr later, and DMBA-deoxyribonucleoside products from the DNA of the tissues were separated on Sephadex LH20 columns. The extent to which the major DMBA-DNA adduct was formed in vivo varied considerably in both maternal and fetal organs. In the mother, concentrations of this adduct (disintegrations/minute per micromole of adenine) were highest in the small intestine (19,278), liver (11,576), and lung (10,711), followed by spleen (7,757), kidney (3,656), and brain (1,328). Concentrations in fetal intestine (12,703) and liver (9,681) were much lower than those in the maternal organs, but the concentration in fetal brain (3,292) was 2.5 times higher than that in maternal brain DNA, possibly due to differences in DMBA uptake through the blood-brain barrier. The results indicate that there is no significant placental barrier to DMBA or DMBA metabolites involved in DNA binding and that rat fetuses participate in the metabolic formation of the ultimate carcinogen. (26 refs)

78-5537 **DNA Labeling Index and Structure of the Mammary Gland as Determinants of its Susceptibility to Carcinogenesis.** (Eng) Russo, J. (Experiment thology Lab., Dept. Biology, Michigan Cancer Found 110 E. Warren Ave., Detroit, MI, 48201); Russo, I. H. *Cancer Inst* 61(6): 1451-1459; 1978.

In a study of 7,12-dimethylbenz(a)anthracene (DMB duced mammary carcinomas, an attempt was made to late the number of mammary gland terminal end-buds terminal ducts (TD), and alveolar buds (AB), togethe their DNA labeling indexes, at the time of DMBA ad tration with the number and types of tumors induced carcinogen. Young virgin (55 days old), old virgin (18 old), and multiparous (180 days old) Sprague-Dawle were inoculated iv with methyl-^{3}H-thymidine (2.5 and killed 1 hr later (Group 1). The number of ducts an and the DNA labeling index in the epithelial cells of structures were compared with the number of t developing in age-matched mice (Group 2) 22 wk they received DMBA (10 mg intragastrically) thymidine. The number of TEB, TD, and labele was highest in young virgins, and 100% of the that developed in these animals were adenocarcin The older virgins had fewer TB and TD and labeled cells, and these rats developed fewer ade cinomas (63%). Glands of multiparous rats contain TEB, a small number of TEB, and few labelled cells; rats had the lowest incidence (21%) of adenocarcin In the old virgins and multiparous rats, the inci of fibroadenomas was 36% and 79%, respectively tumor latency period was longer for these rats than f young virgins. The percentage of DNA-labeled AB time of DMBA administration was 50% in young v compared with 0.5% in old virgins and 0.9% in multip rats. These results demonstrate that susceptibility to ca gens is correlated with the density of TEB and TD and DNA labeling indexes. (69 refs)

78-5538 **DMBA Induced Papillomas in Congen Athymic (Nude) and Hereditarily As (Dh/+) Mice: Contrasts and Comparisons with Immun cally Intact Littermates.** (Eng) Gershwin, M. E. (S Rheumatology-Clinical Immunology, Dept. Medicine thology, Univ. California, Sch. Medicine, Davis, CA, 9 Ikeda, R. *Dev Comp Immunol* 2(3): 529-537; 1978.

The induction of papillomas by dimethylbenz(a)anthr (DMBA) and hereditarily asplenic (Dh/+) mice and i immunologically normal littermates [nude/+ and B6 (+/+) respectively]. DMBA (200 μg) was applied weekly for 20 wk to the shaved flank skin of the mice incidence of papillomas at the end of 20 wk was 17% a the nude mice, 78% among the nude/+ mice, 21% a the Dh/+ mice, and 75% among the B6.CBA (+/+) Furthermore, the number of papillomas/mouse and t mor growth rate were greater for the normal mice th their immune-deficient littermates, and the tumor l

d was shorter. Nude/+ skin that was transplanted to mice and then painted with DMBA reacted in a manner ar to that of nude skin. The data suggest that the im- system has a major role in stimulating papilloma induc- (22 refs)

539 **Resistance to a Transplantable Rat Mammary Tumor (DMBA 8BT) after Pre-treatment with eneic Fetal Cells.** (Eng) Cocuzzi, E. (Dept. Clinical Bio- istry, Sunnybrook Medical Centre, Univ. Toronto, 2075 iew Ave., Toronto, Ontario, Canada M4N 3M5); Kel- J. A. *Res Commun Chem Pathol Pharmacol* 20(2): 08; 1978.

effect of presensitization to fetal antigens on the trans- ability of a chemically induced rat mammary tumor, the BA 8BT adenocarcinoma (induced by feeding female ler 344 rats with 7,12-dimethylbenz(a)anthracene), was tigated in female Fischer 344/Mia albino rats. The rats immunized with mid-term syngeneic fetal cells (3 sc ions of 5 x 10^5 viable cells at 7-day intervals) and inject- th tumor cells 11 days after the final fetal cell immuniza- This immunization schedule provided complete protec- against an inoculum of up to 5 x 10^5 tumor cells, an unt that leads to a 100% tumor take without pretreat- . No difference in tumor take, growth rate, or survival observed between virgin and retired breeder rats. Mul- ity does not protect against this tumor model. (4 refs)

540 **Cultivation of Human Adult Skin Fibroblasts & Induction of Malignant Transformation with Dimethylbenz(a)anthracene.** (Eng) Gokhale, J. A. (Bi- Div., Cancer Res. Inst., Tata Memorial Centre, Bom- 400 012, India); Rao, K. V.; Bhat, A. V.; Bapat, C. V. *an J Exp Biol* 16(5): 549-551; 1978.

effect of 7,12-dimethylbenz(a)anthracene (DMBA) on blasts from the skin of a patient with mucopolysac- idosis was studied to examine the possible susceptibility netically deficient human cells to chemical carcinogens. cells exhibited a typical fibroblastic morphology and nor- and orderly growth with contact inhibition. Exposure of age 5 cells to DMBA (0.1 μg/ml) for 72 hr resulted in oss of cell orientation and the occurrence of small colo- with a criss-cross growth pattern. However, these cells not induce tumors when inoculated (1 x 10^6 cells) into cheek pouch of golden hamsters. In another experiment, age 12 cultures were exposed to UV light (160 ergs/- mm^2 at 250-260 mm) for 30 sec, followed immediately DMBA (10 μg/ml). These fibroblasts piled up into an ular multilayer with increased saturation density. These DMBA-treated cells produced a solid 1-cm nodule very h like a tumor, when inoculated into the hamster cheek ch. In this study, certain morphological, behavioral, and hemical changes occurred in the cells that were indicative of malignant change but did not yield a proliferative population. However, these observations suggest that cells with a genetic defect may be a feasible model for the induction of malignant transformation in vitro. (12 refs)

78-5541 **Transplacental Penetration of 7,12-Dimethylbenz(a)anthracene and Its Distribution in Organs of the Rat Fetus.** (Rus) Baranova, L. N. (Lab. Biophysics, N. N. Petrov Scientific Res. Inst. Oncology, Leningrad, USSR); Aleksandrov, V. A. *Biull Eksp Biol Med* 86(10): 477-479; 1978.

The distribution and elimination of 7,12-dimethylbenz(a)anthracene (DMBA) in maternal and fetal rat organs were studied 5-300 min after iv injection of a single 15-mg/kg dose to white rats on day 21 of pregnancy. The DMBA level reached its max in the liver (45 μg/kg) and in the placenta (6.3 μg/kg) at 10-15 min after injection. The DMBA concentration peaked at 1 hr after injection in the fetal tissues, and only trace amounts were found after 5 hr. The DMBA levels in the fetus 1 hr after injection were 4.7 μg/kg in the liver, 2.4 μg/kg in the kidney, 2.2 μg/kg in the lungs, 1.5 μg/kg in the brain, 1.8 μg/kg in the intestine, and 1.1 μg/kg in the carcass. The findings do not correlate with data on the preferential formation of renal and nervous system tumors following transplacental exposure to DMBA. (4 refs)

78-5542 **Differentiation of Malignant Myoblasts in 7,12-Dimethylbenz(a)anthracene-induced Rhabdomyoblastomas. An Electron Microscopic Study.** (Eng) Markov, D. V. (Regeneration Res. Lab., Bulgarian Acad. Sciences, 1431 Sofia, Bulgaria); Hadjiolov, D. C. *Arch Geschwulstforsch* 48(6): 521-537; 1978.

Samples of necrotic tissue and rhabdomyoblastomas induced in male Syrian hamsters by im injections of 1 mg 7,12-dimethylbenz(a)anthracene were analyzed by light and electron microscopy at various times postinjection. Early neoplastic growth was characterized by the presence of small cells (SC) and long spindle-shaped cells (LSSC). SC always possessed a single heterochromatic nucleus with a small, compact nucleolus. The cytoplasm was characterized by well-developed Golgi apparatus (GA), dense, tubular smooth endoplasmic reticulum (SER), and almost complete absence of granular endoplasmic reticulum (GER). Also present were numerous centrioles and small lysosomelike bodies. These features were indicative of a low level of biosynthetic activity in these cells; this conclusion was supported by their low degree of differentiation. SC were hypothesized to be the precursors of the LSSC, which had the characteristics of elevated biosynthetic activity. Variable numbers of large euchromatic nuclei were present with multiple nucleoli. The cytoplasm was characterized by well-developed GA and GER, varying amounts of cytofilaments, and numerous ribosomes. Occasional LSSC contained neither GA nor cytofilaments but showed GER

with a dense substance accumulated within enlarged cisternae. These LSSC had a tendency to fuse and resembled normal myoblasts morphologically and developmentally, but they did not normally form myofibrils. It is concluded that the SC formed the proliferative cell compartment of the tumor. (67 refs)

78-5543 **Vasopressin Stimulation of Acetate Incorporation into Lipids in a Dimethylbenz(a)anthracene-induced Rat Mammary Tumor Cell Line.** (Eng) Monaco, M. E. (Medicine Branch, NCI, Bethesda, MD, 20014); Lippman, M. E.; Knazek, R.; Kidwell, W. R. *Cancer Res* 38(11, part 2): 4101-4104; 1978.

The possibility that the effects of rat prolactin B-1 (PL) on acetate incorporation into lipids are caused by vasopressin (VP) contamination was investigated in a cloned cell line (WRK-1) derived from a dimethylbenz(a)anthracene-induced rat mammary tumor. There was a twofold increase in ^{14}C-acetate incorporation with PL alone. In the presence of insulin (5×10^{-7} M), the effect was increased 10-fold. Concentrations of PL required for max stimulation in both instances were 1-5 μg/ml, and max activity was not seen until 36 hr after addition of the hormones. Rat growth hormone B-3 elicited a response similar to that with PL. More purified rat PL 1-2, human growth hormone HS-2019G, and ovine PL P-S-12 had minimal effects on the incorporation of ^{14}C-acetate into lipids. Activity appeared to be inversely related to the purity of the preparation. Both VP (10^{-10} M; 20 micro units/ml) and oxytocin elicited the response observed with impure PL and growth hormone, but 100 times more oxytocin was required. This suggests that VP is the physiologically relevant hormone. Following filtration of rat PL, virtually all the activity resided in the low-mol-wt filtrate. The activity observed in this system would require a minimal VP contamination of 0.02%, which is well within the concentrations detected by radioimmunoassay in the rat PL and growth hormone B-3 preparations used in this study. Thus, VP is probably responsible for some of the activity observed with both rat PL and growth hormone. (11 refs)

78-5544 **Synthesis of Potentially Estrogenic Carcinogens: 7,12-Dimethylbenz(a)anthracene-3,9-diol.** (Eng) Morreal, C. E. (Dept. Breast Surgery, Roswell Park Memorial Inst., Buffalo, NY, 14263); Bronstein, R. E. *J Chem Eng Data* 23(4): 354-356; 1978.

The synthesis of a diphenolic derivative of 7,12-dimethylbenz(a)anthracene, 7,12-dimethylbenz(a)anthracene-3,9-diol, from 4-methoxyphthalic anhydride and 6-methoxy-2-bromonaphthalene is described. The diol has the potential to behave as an estrogen and as a carcinogen. (5 refs)

78-5545 **The Effect of Altered Thyroid State on P tin Binding to Liver and 7,12-Dimethyl (a)anthracene-induced Mammary Tumors in Rats.** Smith, R. D. (Dept. Biochemistry, Univ. Rochester M Center, Rochester, NY, 14642); Hilf, R.; Senior, A. E *Soc Exp Biol Med* 158(4): 517-520; 1978.

The effect of thyroid state on prolactin (PRL) binding t and on 7,12-dimethylbenz(a)anthracene (DMBA)-in mammary tumors was studied in female Sprague-D rats. Rats were given 5 mg DMBA/wk for 5 wk by g intubation. Rats bearing tumors of sufficient size (2-3 were made hypothyroid by administration of prop ouracil (0.1% wt/vol in the drinking water for 21 da hyperthyroid by injections of L-thyroxine (75 μg/100 daily for 10 days). Neither hypo- nor hyperthyroidism s cantly influenced the growth rates of estab DMBA-induced tumors, PRL binding to these tumo plasma PRL in tumor-bearing rats. PRL binding to membrane particles was reduced 85% following either or hyperthyroid induction in tumor-bearing rats. The p logical role of the liver PRL receptors remains unknow refs)

78-5546 **Effect of Oophorectomy on Estrogen Rec in Rat Mammary Tumors Induce 7,12-Dimethylbenz(a)anthracene.** (Eng) Tominaga, T. Surgery, Tokyo Metropolitan Komagome Hosp., 3- Honkomagome, Bunkyo-ku, Tokyo, Japan); Kitamur Tei, N. *Biken J* 20(3/4): 143-145; 1977.

The relationship between the response of 7,12-dimethyl (a)anthracene (DMBA)-induced rat mammary tumors phorectomy and the presence of estrogen receptors (E the tumor tissue was examined. Iv administration mg/kg DMBA to female Sprague-Dawley rats resulte 100% tumor incidence. Small sections of tumor removed and tested for the presence of ER. Bilater phorectomy was then performed, the residual tumors removed 7-11 days later, and tests for ER were rep Before oophorectomy, ER were found in 18/33 tumor special correlation was noted between the histologic ferentiation of the mammary carcinomas or the time of induction after DMBA adminstration and the preser ER. Oophorectomy resulted in the disappearance of 17/18 tumors within several days of surgery. ER wer present in the remaining rat 7 day after oophorectom but one of the 18 tumors with ER decreased in size 7-1 after oophorectomy. Of the 15 tumors without ER, 4 9 regressed, and 2 remained unchanged following oop tomy; no ER were found in any of these tumors after c tion. Since a tumor that decreased in size after oophore lost its ER completely within 10 days and another without ER increased in size after oophorectomy, it wa cluded that tumor growth was not dependent on ovaria mones alone. Further studies in which rats received es ol-17β suggested that tumor growth is closely related this compound, and not with the presence of ER. (9

5547 **Synthesis and Carcinogenic Activity of 5-Fluoro-7-(oxygenated methyl)-12-methylz(a)anthracenes.** (Eng) Newman, M. S. (Chemistry Dept., io State Univ., Columbus, OH, 43210); Fikes, L. E.; Ham, M. M.; Kannan, R.; Sankaran, V. *J Med Chem* 21(10): 6-1078; 1978.

luoro-7-(oxygenated methyl)-12-methylbenz(a)anthraes were synthesized and their carcinogenicity was assayed ats. Groups of 18 male Fischer rats were injected sc with 2-dimethylbenz(a)anthracene (DMBA: single injection of mg), 5-fluoro-7-hydroxymethyl-12-methylbenz(a)anthrae (5-F-7-OH-DMBA: 2.3 mg 1x/wk for 4 wk), or luoro-7-acetoxymethyl-12-methylbenz(a)anthracene (5-F-)Ac-DMBA: 2.7 mg 1x/wk for 4 wk). Three of the eight- rats injected with DMBA had sarcomas at the injection by 6, 9, and 16 mo after injection. By contrast, only 1/18 s that had received 5-F-7-OH-DMBA and 0/18 that had eived 5-F-7-OAc-DMBA developed sarcomas by the end 16 mo. In another experiment, male Sprague-Dawley rats re injected sc with 5-fluoro-7,12-benz(a)anthraquinone F-BAQ); 5-F-7-OAc-DMBA, or 5-F-7-OH-DMBA (0.1 cromole 3x/wk for 30 doses, beginning at age 30 days). ne of the rats injected with 5-F-7-OH-DMBA, 3/13 injectwith 5-F-7-OAc-DMBA, and 1/12 injected with 5-F-BAQ veloped sarcomas at the injection site. Since neither -7-OH-DMBA nor 5-F-7-OAc-DMBA was appreciably rcinogenic, the carcinogenic metabolism of DMBA proba does not involve attack at the 7-methyl group. The nethyl group merely serves to block a detoxification meolism that is initiated at the 7 position. When the detoxifiion pathway is blocked, the cancer-producing mechanism become effective. (22 refs)

5548 **Metabolic Activation of Dibenzo(a,h)anthracene and Its Dihydrodiols to Bacterial Mutans.** (Eng) Wood, A. W. (Dept. Biochemistry and Drug Meolism, Hoffmann-LaRoche Inc., Nutley, NJ, 07110); vin, W.; Thomas, P. E.; Ryan, D.; Karle, J. M.; Yagi, H.; ina, D. M.; Conney, A. H. *Cancer Res* 38(7): 1967-1973; 78.

benz(a,h)anthracene (DBA) and the three metabolically ssible trans-dihydrodiols of DBA were tested for utagenicity toward *Salmonella typhimurium* strain TA100. e tests were performed in the presence of hepatic misomes from Aroclor 1254-pretreated rats or in the cytorome P-450-dependent monooxygenase system isolated d purified to near homogeneity from these microsomes. ith either enzyme system, the 3,4-dihydrodiol was activat to products that were more mutagenic than the metaboes of DBA or its 1,2- and 5,6-dihydrodiols. With misomes, but not with the purified monooxygenase system, e 5,6-dihydrodiol was also activated to products that were ghly mutagenic. However, significant activation was seen ly when high concentrations of the 5,6-dihydrodiol were cubated with relatively high amounts of enzyme. Saturation of the double bond at position 1,2 of the 3,4-dihydrodiol produced a tetrahydrodiol that was poorly activated in either metabolic activation system. The high activity of the 3,4-dihydrodiol in both systems and the importance of the double bond in position 1,2 of the dihydrodiol strongly suggest that a bay-region 3,4-diol-1,2-epoxide is a biologically important active metabolite of DBA, thereby providing support for the bay region theory. (39 refs)

78-5549 **Determination of Benzo(a)pyrene in a Filtered Retort Water Sample by Solid-Surface Fluorescence.** (Eng) Hurtubise, R. J. (Dept. Chemistry, Univ. Wyoming, Laramie, WY, 82071); Phillip, J. D.; Skar, G. T. *Anal Chim Acta* 101(2): 333-338; 1978.

A method is described for determining benzo(a)pyrene (BP) in filtered retort water from an in situ oil shale process by liquid-liquid extraction, dry-column chromatography, thin-layer chromatography, and fluorescence spectrometry. BP was identified by detecting its fluorescence directly from chromatoplates. The accuracy and precision of the method were good; the detection limit was approx 0.08 ppb. (17 refs)

78-5550 **Factors Affecting the Binding of Polycyclic Aromatic Hydrocarbons to Human Embryo Cells, and Transformable and Non-transformable Hamster Embryo Cells.** (Eng) Raineri, R. (Chemical Carcinogenesis Program, NCI, Frederick Cancer Res. Center, Frederick, MD, 21501); Poiley, J. A.; Hillesund, T.; Pienta, R. J. *Chem Biol Interact* 22(2/3): 257-270; 1978.

The effects of various factors on the binding of three polycyclic aromatic hydrocarbons to human (HuEC) and Syrian golden hamster embryo cells (HaEC) were studied. The binding of 7,12-dimethylbenz(a)anthracene (DMBA) to HaEC DNA, RNA, and protein was max after 22 hr of treatment. In contrast, binding to HuEC macromolecules increased for at least 55 hr. Treatment of HaEC at 100% confluence resulted in much less binding than treatment at 70% confluence, whereas with HuEC the binding increased or remained constant following treatment at the greater confluence. The transforming frequency of HaEC decreased with increasing population doubling number (PDN): binding of DMBA to hamster embryo DNA, RNA, and protein decreased approx 100-fold between PBN's 8 and 20. In transformable cell cultures, DMBA was bound to HaEC DNA to a greater extent than to RNA or protein. The binding of DMBA to HuEC DNA was low at population doubling 30 and did not change with increasing PDN. The binding to HuEC RNA was also low, but the binding to protein increased 2.5-fold between PDN's 5 and 70, after which binding decreased sharply. The binding of DMBA to nucleic acids was much greater than binding by dibenz(a,h)anthracene or dibenz(a,c)anthracene, both of which had low binding values at all PDN's tested. Therefore, the best correlation of binding with carcinogenici-

ty and transforming activity was observed with DMBA. (16 refs)

78-5551 **Fluorometric Detection of Carcinogen Binding.** (Eng) Rho, J. H. (Univ. California, Schs. Medicine and Pharmacy, Los Angeles, CA); Okigaki, T.; Bonner, J. *In: Prevention and Detection of Cancer. Proceedings of the Third International Symposium on Detection and Prevention of Cancer Held by the International Study Group for the Detection and Prevention of Cancer in New York, April 26 - May 1, 1976.* International Study Group for the Detection and Prevention of Cancer. (New York, NY): Vol. 2 (Part 1), 2404 pp.; 1365-1374; 1978.

The results of a three-dimensional fluorometric analysis of benzo(a)pyrene (BP) metabolites bound to the chromatin components of cultured Syrian golden hamster embryonic lung cells are reported. The cells were exposed to ^{3}H-BP (0.5 μg/ml) for 24 hr. The chromosomal constituents were separated by centrifugation and electrophoresis into the DNA fraction, proteins tightly bound to DNA, and 4 M NaCl-soluble proteins. The three-dimensional fluorescence spectra revealed that the NaCl-soluble proteins were bound predominantly with monohydroxylated BP, the tightly bound proteins with *cis*-7,8-diol-9,10-epoxy-BP, and the DNA with BP itself. These results indicate that a BP metabolite similar to the *cis*-7,8-diol-9,10-epoxide forms a molecular complex between various nonhistone chromosomal proteins and DNA through a carcinogenic reaction of the metabolite. (20 refs)

78-5552 **Glucuronidation of Benzo(a)pyrene in Hamster Embryo Cells.** (Eng) Nemoto, N. (Dept. Experimental Pathology, Cancer Inst., 1-37-1, Kami-Ikebukuro, Toshima-ku, Tokyo 170, Japan); Hirakawa, T.; Takayama, S. *Chem Biol Interact* 22(1): 1-14; 1978.

Cultures of Syrian hamster embryo cells were exposed to 3.75 or 37.5 nanomoles (nmol)/ml of ^{3}H-labeled benzo(a)pyrene (BP), and the formation of BP metabolites before and after treatment of the medium with β-glucuronidase (GU) was analyzed by thin-layer chromatography (TLC) and high-pressure liquid chromatography (HPLC). The ratio of radioactivity (RA) in the aqueous phase to that in the organic phase increased with time of incubation. After incubation for 48 hr with 3.75 nmol/ml BP, 92.5% of the RA was found in the aqueous phase, but with 37.5 nmol/ml BP, 53.4% of the RA remained in the organic phase. Medium containing the higher dose of BP was extracted with ethyl acetate, and BP metabolites in the organic phase were separated by HPLC. The major metabolites eluted were the 9,10-diol and 7,8-diol; the amount of 4,5-diol was negligible. After treatment of the medium with GU, however, the major oxygenated metabolites were shown by TLC to be phenols, with the amount of 3-hydroxy-BP being greater than that of 9-hydroxy-BP. GU also released 9,10-diol and 7,8-diol, but m of these diols were in free form in the medium. With the lo BP concentraton, the metabolic profile was different: di and phenols were barely detectable, and almost nothing cept intact BP was found. However, on treatment with G large amounts of phenols and small amounts of diols peared. The results show that in hamster embryo cells, is mainly metabolized to conjugates of phenols with glu ronic acid. (29 refs)

78-5553 **Modulation of the Binding of the Carcino Benzo(a)pyrene to Rat Liver DNA In Vivo Selective Induction of Microsomal and Nuclear Aryl Hyd carbon Hydroxylase Activity.** (Eng) Viviani, A. (Inst. T icology, Federal Inst. Technology, CH-8603 Schwerzenba Zurich, Switzerland); Lutz, W. K. *Cancer Res* 38(1 4640-4644; 1978.

The influence of microsomal and nuclear aryl hydrocarb hydroxylase (AHH) activity on the covalent binding of ^{3}H]benzo(a)pyrene to rat liver DNA was evaluated in vi Phenobarbital treatment (1 g/liter in drinking water) indu microsomal AHH in male Sprague-Dawley rats to 160% control. This treatment also increased DNA binding 190%, but left the nuclear activity unchanged. Nuclear AH was induced to 150% of control by dieldrin treatment mg/kg/day, ip), and binding was decreased to 75%, when the microsomal AHH was at control level. The increas effect of microsomal AHH induction as well as the decreas effect of nuclear AHH induction on binding was shown cle ly when the data on individual rats were used to solve following equation: binding = a*(microsomal AHH) b*(nuclear AHH) + C. Multiple linear regression analy with the data from 10 animals resulted in positive values a and c, a negative value for b, and a good multiple corr tion coefficient of r = 0.974. Pretreatment of the rats w 3-methylcholanthrene (20 mg/kg/day, ip) induced micro mal AHH to 380% of control and nuclear AHH to 59 and increased binding to 175%. The binding was higher th that predicted by the formula, probably because the incre ing influence of induced microsomal AHH overshadowed decreasing effect of nuclear AHH. The results show that binding of a foreign compound to DNA in vivo is depend not only on microsomal enzyme activities but also on nucl activities, even if the latter are considerably lower than th of microsomes. (21 refs)

78-5554 **[^{3}H]Benzo(a)pyrene Metabolism in Trach Epithelial Microsomes and Tracheal Organ C tures.** (Eng) Mass, M. J. (Dept. Pathology, Sch. Medici Univ. North Carolina at Chapel Hill, Chapel Hill, N 27514); Kaufman, D. G. *Cancer Res* 38(11, part 3861-3866; 1978.

^{3}H-Benzo(a)pyrene (BP) metabolism was studied in Syr

en hamster tracheal epithelial microsomes and tracheal
n cultures. Microsomal BP metabolism was induced by
reatment of tracheas with 5 μM BP in organ culture. The
irent Km's for the induced and constitutive (uninduced)
monooxygenase were not significantly different and were
μM. However, the induced enzyme had a Vmax of 86
moles (pmol) product/mg microsomal protein/min,
reas the constitutive enzyme had a value of 31
ol/mg/min, a 2.8-fold increase. Microsomes from B-in-
ed and uninduced tracheas mediated the binding of 12.84
)$^{-3}$ and 8.06 x 10^{-4} pmol BP/μg DNA/μg tracheal mi-
omal protein respectively, during incubation at 37 C for
in. High-pressure liquid chromatography revealed that
major metabolites produced by tracheal microsomes in-
ated with 2 μM ^{3}H-BP for 30 min were diols, quinones,
phenols of BP. After 24 hr of incubation with ^{3}H-BP,
metabolites formed in organ cultures of induced tracheas
e largely tetrols, triols, and the *trans*-
)-dihydro-9,10-dihydroxybenzo(a)pyrene. The disparity
ween metabolites produced in these two systems may be
ted to coupled secondary metabolic reactions that occur
n prolonged incubation in the intact cells of organ cul-
es. (38 refs)

5555 **Comparative Studies of the Carcinogenic Polycyclic Aromatic Hydrocarbon Levels in Smoked odstuffs in Hungary and in East Germany.** (Hun) Soos, (Urszagos Elelmezes- es Taplalkozastudomanyi Intezet, dapest, Hungary); Fritz, W. *Egeszsegtudomany* 21(3): -285; 1978.

irty-two kinds of commercial and homemade smoked meat oducts from Hungary and 29 kinds of smoked meat pro-cts from East Germany, as well as smoked cheese and fish mples, were analyzed for benzo(a)pyrene (BP) and other cinogenic and cocarcinogenic polycyclic aromatic hydro-bons (PAH) by UV spectrophotometry and spectro-ometry. The av BP level in the commercial meat pro-cts was 0.6 μg/kg in Hungary and 0.43 μg/kg in East rmany. The BP levels in the home-smoked meat products re somewhat lower in both countries (0.74 μg/kg in Hun-y and 0.76 μg/kg in East Germany). The BP level was μg/kg in 8/32 Hungarian samples (2 commercial, 6 me-smoked) and in 4/29 samples from East Germany (1 mmercial, 3 home-smoked). The total PAH level was newhat lower in cold-smoked meat products than in those oked at 40 or 100 C in both countries. The av BP levels re 0.95 μg/kg in smoked cheese, 8.65 μg/kg in smoked n with skin, and 1.39 μg/kg in skinned smoked fish. The dings indicate that the permissible BP level in smoked food ould be set at 1 μg/kg in both countries. (20 refs)

-5556 **Asbestos-mediated Membrane Uptake of Benzo(a)pyrene Observed by Fluorescence Spec-oscopy.** (Eng) Lakowicz, J. R. (Freshwater Biological Inst., Univ. Minnesota, County Roads 15 and 19, P.O. Box 100, Navarre, MN, 55392); Hylden, J. L. *Nature* 275(5679): 446-448; 1978.

The ability of asbestos and silica to adsorb benzo(a)pyrene (BP) and to deliver the adsorbed carcinogen to a model membrane was investigated by fluorescence spectroscopy. The surface area of the silica sample was 381 m^2/g, and most particles were 1.5-15 μm in diameter (av 3 μm). The surface area of the asbestos sample was 5.6 m^2/g, and the particle size was 1.5-10 μg (av 2 μg). Particulate samples containing BP were prepared by mixing the particulate with a benzene soln of BP (0.1-3.0 mg BP/g particulate), followed by evaporation of the benzene under reduced pressure. The amounts of BP adsorbed to silica and asbestos were 85% of the amount added. Although the surface area of the asbestos sample was 60 times less than that of the silica sample, asbestos was more effective than silica in transferring BP to the membrane at all BP-to-particulate wt ratios examined. Asbestos or silica, when added to preformed microcrystals of BP in buffer, did not increase the rate of BP membrane uptake, indicating that only BP that is adsorbed to the particles displays an increased rate of membrane uptake. It is concluded that increased cellular exposure to carcinogens, resulting from the presence of particulates that can adsorb and deliver these carcinogens to the cell, may be involved in the process of cocarcinogenesis. (20 refs)

78-5557 **Inhibition of Benzo(a)pyrene Binding to DNA in Cultured Human Bronchi.** (Eng) Harris, C. C. (Human Tissue Studies Section, NCI, Building 37, Room 3A07, Bethesda, MD, 20014); Autrup, H.; van Haaften, C.; Connor, R.; Frank, A. L.; Barrett, L. A.; McDowell, E. M.; Trump, B. F. *In: Prevention and Detection of Cancer. Proceedings of the Third International Symposium on Detection and Prevention of Cancer Held by the International Study Group for the Detection and Prevention of Cancer in New York, April 26 - May 1, 1976.* International Study Group for the Detection and Prevention of Cancer. (New York, NY): Vol. 2(Part 1), 2404 pp.; 1359-1364; 1978.

The binding of benzo(a)pyrene (BP) to cultured human bronchial cell DNA was shown to be reduced by inhibitors of BP metabolism and inhibitors of chemical carcinogenesis. Cells from specimens of human bronchi removed at 'immediate autopsy' or during surgery from 9 patients with and from 5 patients without lung cancer were cultured. After 7 days, the cultures were exposed for 24 hr to ^{3}H-BP (25 Ci/mmole) either with or without (controls) one of the following: 7,8-benzoflavone (BF) (BF: 20 μM), vitamin E (VE: 10 and 100 μM), disulfiram (DS: 10 and 100 μM) or vitamin A (VA: 3 and 30 μM). Compared with controls, the level of bound BP was decreased by BF and, to a lesser extent, by DS (100 μM) and VE (100 μM). The binding level was not significantly altered by VA, DS (10 μM), or VE (10 μM). There were no binding differences between cultures from cancer or non-cancer patients. The results show that it may be possible to

quantify and modify the interaction of chemical carcinogens with specific human target tissues in a controlled experimental setting. (17 refs)

78-5558 **Fluorescence Studies of Benzo(a)pyrene Uptake by Cultured Macrophages and Lymphocytes.** (Fre) Salmon, J. M. (Laboratoire de Chimie physique, Centre Universitaire, avenue de Villeneuve, 66025 Perpignan, France); Thierry, C.; Serrou, B.; Viallet, P. *C R Acad Sci D (Paris)* 287(4): 345-348; 1978.

The kinetics of benzo(a)pyrene uptake by human lymphocytes and mouse macrophages was studied in vitro by microspectrofluorometry. The uptake appeared to be a first-order reaction. A fluorescent metabolite was detected in the macrophages, but not in the lymphocytes. (8 refs)

78-5559 **Modification of the Mutagenicity of Benzo(a)-pyrene on Bacteria by Substrates of Enzymes Producing Water Soluble Conjugates.** (Eng) Nemoto, N. (Dept. Experimental Pathology, Cancer Inst., 1-37-1, Kami-Ikebukuro, Toshima-ku, Tokyo 170, Japan); Takayama, S.; Nagao, M.; Umezawa, K. *Toxicol Lett* 2(4): 205-211; 1978.

The effects of enzyme substrates that produce water-soluble conjugates on the mutagenicity of benzo(a)pyrene (BP) to *Salmonella typhimurium* strains TA98 and TA100 were studied. At a BP concentration of 2.5 μg/plate, the number of revertants decreased with increasing concentration of uridine 5′-diphosphoglucuronic acid (UDPGA) in the incubation mixture. However, at a BP concentration of 10 μg/plate, the number of revertants was slightly increased in the presence of UDPGA; this increase was greater with TA98 than with TA100. The mutagenicity of BP (5 or 10 μg/plate) was also enhanced by ATP, whereas glutathione (GSH) reduced the number of revertants. UDPGA and, to a lesser extent, ATP inhibited the apparent aryl hydrocarbon hydroxylase (AHH) activity of the S-9 liver fraction from polychlorinated biphenyl-treated rats. GSH had no significant effect on this activity. Thus, one reason why results on the mutagenicities of certain chemicals vary is that UDPGA, ATP, and GSH, present as contaminants in the S-9 fraction, influence the reactions of detoxifying enzymes in this fraction. (23 refs)

78-5560 **The Effect of Overcrowding Stress on the Carcinogen-metabolizing Enzymes of Rats.** (Eng) Capel, I. D. (Res. Dept., Marie Curie Memorial Foundation, The Chart, Oxted, Surrey RH8 0TL, England); Williams, D. C. *ICRS Med Sci (Cancer)* 6(8): 329; 1978.

The effect of overcrowding (OC) on the hepatic microsomal enzyme system responsible for activating benzo(a)pyrene and on the plasma disposition of antipyrine [monitored as an e mate of in vivo aryl hydrocarbon hydroxylase (AHH) acti ty] was determined in Spraque-Dawley rats. OC decrea the rate and amount of antipyrine absorption. The plas cortisol level was max on day 4 of OC, when there wa fourfold increase in the in vitro AHH level. Although increased AHH activity, there was a gradual adaptation this form of stress. (5 refs)

78-5561 **Binding of Benzo(a)pyrene at the 1,3,6 Positi to Nucleic Acids In Vivo on Mouse Skin and Vitro with Rat Liver Microsomes and Nuclei.** (Eng) Rog E. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical C ter, 42nd and Dewey Ave., Omaha, NB, 68105); Roth, Katomski, P.; Benderson, J.; Cavalieri, E. *Chem Biol Inter* 22(1): 35-51; 1978.

Double-label studies of benzo(a)pyrene (BP) binding to cleic acids were undertaken to determine if binding of BP nucleic acids occurs at the 1, 3, and 6 positions of BP a if tritium loss from a specific position is a valid measure binding at that site. Tritium loss from (6-^{3}H,^{14}C)BP, (1,3- ^{14}C)BP, (1,3,6-^{3}H,^{14}C)BP, (6,7-^{3}H,^{14}C)BP, and (7-^{3}H,^{14}C) was studied in vitro using liver nuclei and microsomes fr 3-methylcholanthrene-induced Sprague-Dawley rats and vivo on Charles River CD-1 mouse skin. The relative triti loss from (^{3}H,^{14}C)BP was measured after binding to s DNA and RNA, to nuclear DNA, and to native and de tured calf thymus and rat liver DNA's and poly(G) by crosomal activation. In skin, nuclei, and microsomes plus tive DNA, virtually all BP binding occurred at positions 3, and 6; with microsomes plus denatured DNA or poly(BP showed no binding at position 6 and little if any at po tions 1 and 3. In vivo and in isolated nuclei, binding at po tion 6 predominated. There was little loss of tritium fr position 7; this was expected, because binding at this positi is not thought to occur. This confirms the interpretation loss of tritium as an indication of binding at a given positi The results demonstrate that the use of microsomes to a vate BP is not a valid model system for delineating the in v mechanism of BP activation, and they support previous e dence for one-electron oxidation as the mechanism of acti tion of hydrocarbons in binding to nucleic acids. (44 ref

78-5562 **Metabolism of Benzo(a)pyrene and Identifi tion of the Major Benzo(a)pyrene-DNA A ducts in Cultured Human Colon.** (Eng) Autrup, H. (Hum Tissue Studies Section, Carcinogenesis Res. Program, N Building 37, Room 3A09, Bethesda, MD, 20014); Harris, C.; Trump, B. F.; Jeffrey, A. M. *Cancer Res* 38(11, part 3689-3696; 1978.

The metabolism of benzo(a)pyrene (BP) in cultured non morous colonic tissue from patients with and without colo cancer was investigated. Also studied were the effects of lit

lic acid (LC) and taurodeoxycholic acid (TDC), second- bile acids, on the binding level of BP to cellular mac- olecules and on the metabolite profile of BP. Cultured nan colonic tissue exposed to 1.5 μM BP for 24 hr pro- ed two DNA-BP adducts: the major adduct (72%-100%) formed between the 10 position of BP diol-epoxide I and 2-amino group of guanine; the minor adduct was formed ween BP diol-epoxide II and the 2-amino group of gua- e. The major metabolites of BP extracted with ethyl ace- e/acetone from the tissue culture media were 0/8,9)-tetrahydroxy-7,10,8,9-tetrahydro-BP, trans-7,8- ydroxy-7,8-dihydro-BP, and a peak containing ,10/8)-tetrahydroxy-7,10,8,9-tetrahydro-BP, (7/8,9)-tri- droxy -7,8- dihydro-BP, and trans -9,10- dihydroxy- 0-dihydro-BP. The metabolites formed by the cul- ed colon varied among individuals. There was a ght difference ($p < 0.1$) in binding levels between ntumorous tissues from cancer patients (40) and se from noncancer patients (16). In addition, binding lev- of BP to DNA varied five fold among different sections colon from the same patient, with levels being highest in ascending colon. LC significantly ($p < 0.05$) enhanced binding of BP to DNA at concentrations of 0.5 and 1.0 M, but higher concentrations decreased binding. TDC ghtly enhanced binding levels in a dose-dependent manner < 0.05). Apparently, cultured human colon can metabol- BP by pathways similar to those observed in human bron- us and in cells of experimental animals. (67 refs)

-5563 **Lack of Mutagenicity and Putative Carcinogenicity of Several Novel Benzopyrene erivatives.** (Eng) Ashwood-Smith, M. J. (Laboratoire de ologie Physico-Chimique, Universite de Dijon, Ecole Na- onale Superieur de Biologie, Appliquee a la Nutrition et a limentation, Dijon, France); Mitchell, R. H.; Kennedy, A. *Mutat Res* 57(2): 123-125; 1978.

ree benzopyrene derivatives with the same gross structure d the same electronic periphery as benzo(a)pyrene, but ith some alteration in the complete electronic structure, ere tested for mutagenicity in the Salmonella/microsome st using strains TA1537, TA100, and TA98. The three erivatives were trans-12b,12c-dimethyl-12b,12c-dihy- robenzo(a)pyrene, trans-12b,12c-dimethyl-12b,12c-dihy- robenzo(e)pyrene, and trans -13b,13c- dimethyl- 3b,13c-dihydrodibenzo(b,def)-chrysene. These deriva- ves were completely without activity in any of the ree tester strains with or without differing amounts f microsomes (from rats stimulated with phenobar- ital or aroclor). Thus, it is not sufficient for a molecule to ave the same electronic periphery as a known mutagen/car- inogen for it to induce mutagenicity (and probably car- inogenicity). (6 refs)

8-5564 **Reconstitution of Benzo(a)pyrene 4,5-Oxide Reductase Activity by Purified Cytochrome P-450.** (Eng) Yamazoe, Y. (Dept. Pharmacology, Sch. Medicine, Keio Univ., 35 Shinanomachi, Shinjuku-ku, Tokyo 160, Japan); Sugiura, M.; Kamataki, T.; Kato, R. *FEBS Lett* 88(2): 337-340; 1978.

Requirements for the reconstitution of NADPH-dependent benzo(a)pyrene 4,5-oxide (BP 4,5-oxide) reductase activity were examined. Cytochrome P-450 was purified from phenobarbital-treated rat liver microsomes (PB P-450) and from 3-methylcholanthrene-treated rat liver microsomes (MC P-450 and MC P-448). Cytochrome P-450 (MC P-448) and NADPH-cytochrome P-450 reductase were essential requirements for the reconstitution of reductase activity. Lipid was also required for max activity. Using liver microsomes from intact and MC-treated rats as controls, MC P-448 in the reconstituted system exhibited 18- and 6-fold greater activity than intact and MC-treated microsomes, respectively. The addition of riboflavin (100 μM) resulted in a 1.7-fold enhancement of BP 4,5-oxide reductase activity. BP 4,5-oxide was reduced by cytochrome P-450 even in the absence of NADPH and NADPH-cytochrome P-450 reductase if a reducing equivalent, such as reduced methylviologen, was present. In this system, MC P-448 showed the highest activity, followed by MC P-450 and PB P-450. The results suggest that both BP and BP 4,5-oxide bind to a common site in the cytochrome P-450 molecule. (15 refs)

78-5565 **Solubilization of 6-Oxybenzo(a)pyrene Radical by Caffeine and DNA as Studied by Magnetic Resonance. Observation of Intermolecular Charge Transfer.** (Eng) Mishra, K. P. (Dept. Chemistry, Faculty Science, Kyoto Univ., Kyoto 606, Japan); Nosaka, Y.; Akasaka, K.; Nagata, C.; Hatano, H. *Biochim Biophys Acta* 520(3): 679-687; 1978.

The reaction of 6-oxybenzo(a)pyrene (6-OBP) free radical (synthesized from 6-hydroxy-BP) with aqueous caffeine and DNA soln's was investigated using nuclear magnetic resonance (NMR) and electron spin resonance (ESR) spectroscopy. The ESR studies indicated that crystals of 6-OBP radical dissolved in the hydrophobic environment of caffeine molecules and existed as dispersed monomers. In aqueous DNA, 6-OBP radical was seen to bind chemically to the molecule. Comparison of NMR spin-lattice and spin-spin relaxation times in caffeine protons disclosed that a part of the 6-OBP unpaired electron was transferred from the radical to the caffeine molecule. This suggested that the reaction involves the formation of a π-bond. It is concluded that the intermolecular charge pathway is not a major source of stabilization energy of this complex. (24 refs)

78-5566 **Sulfate Conjugation of Benzo[a]pyrene Metabolites and Derivatives.** (Eng) Nemoto, N. (Dept. Experimental Pathology, Cancer Inst., Kami-Ikeburkuro, Toshima-ku, Tokyo, Japan); Takayama, S.; Gelboin, H. V. *Chem Biol Interact* 23(1): 19-30; 1978.

The sulfate conjugation of various metabolites and derivatives of benzo(a)pyrene (BP) was studied using rat liver 105,000 *g* supernatant as an enzyme source. On incubation of 3-OH BP with ^{35}S-Na_2SO_4 and a sulfate activating system, a new compound identified as a sulfate conjugate of 3-OH BP was formed. The reaction required $MgCl_2$ as well as ATP, indicating that the sulfate was activated to 3′-phosphoadenosine-5′-phosphosulfate prior to conjugation. The rate of 3-OH BP conjugation depended in part on the period of preincubation, a 20-min preincubation period giving maximum subsequent conjugation. All of the BP phenols and quinone metabolites formed conjugates with sulfate, whereas the dihydrodiol metabolites showed different reactivities. The sulfate conjugates were more polar than their parent BP derivatives and, except for the quinone conjugates, were easily extracted with ethyl acetate. The role of sulfate conjugation in BP carcinogenesis is discussed. (36 refs)

78-5567 **Lack of Involvement of 6-Hydroxymethylation in Benzo(a)pyrene Skin Tumor Initiation in Mice.** (Eng) Slaga, T. J. (Biology Div., Oak Ridge Natl. Lab., P.O. Box Y, Oak Ridge, TN, 37830); Bracken, W. M.; Viaje, A.; Berry, D. L.; Fischer, S. M.; Miller, D. R. *J Natl Cancer Inst* 61(2): 451-455; 1978.

The skin tumor-initiating activities of benzo(a)pyrene (BP), 6-hydroxymethylbenzo(a)pyrene (6-OH-CH_2-BP), and 6-methylbenzo(a)pyrene (6-CH_3-BP) were compared in female CD-1 mice. Further, the effects of 7,8-benzoflavone (7,8-BF), 1-benzylimidazole, and quercetin on these activities were determined. All mice were initiated with 400 or 800 nanomoles of one of the three BP compounds; 1 wk later, the mice were promoted twice weekly with 10 μg 12-O-tetradecanoylphorbol-13-acetate. BP was a much more effective tumor initiator than 6-OH-CH_2-BP or 6-CH_3-BP, the respective activities of these two compounds being 12.5% and 20% that of BP. The tumor-initiating activity of 6-CH_3-BP was greater than 6-OH-CH_2-BP, but only the latter exhibited a dose-response relationship. The administration of 10, 100, and 200 μg of 7,8-BF 5 min before BP resulted in a 20%, 27%, and 32% inhibition of papillomas per mouse, respectively. The number of mice with tumors was only slightly inhibited by the two higher doses of 7,8-BF. This compound had no effect on 6-OH-CH_2-BP and only slightly inhibited 6-CH_3-BP tumor initiation. Quercetin and 1-benzylimidazole (both, 100 μg) inhibited the number of BP-initiated papillomas per mouse by 28% and 40%, respectively. 1-Benzylimidazole + 7,8-BF 5 min before BP resulted in 40% inhibition. These results indicate that direct 6-hydroxymethylation is probably not an important pathway for the activation of BP in mouse skin. (35 refs)

78-5568 **Atmospheric Reactions of Polycyclic Aromatic Hydrocarbons: Facile Formation of Mutagenic Nitro Derivatives.** (Eng) Pitts, J. N. (Statewide Air Pollution Res. Center, Dept. Chemistry, Univ. California, Riven CA, 92521); Van Cauwenberghe, K. A.; Grosjean, Schmid, J. P.; Fitz, D. R.; Belser, W. L.; Knudson, G Hynds, P. M. *Science* 202(4367): 515-519; 1978.

In order to test the hypothesis that oxidative reaction polycyclic aromatic hydrocarbons in the atmosphere lead to the formation of directly active mutagens, two of experiments were conducted: one in which the carcin benzo(a)pyrene and the noncarcinogen perylene were exposed to pollutant gases under simulated atmospheric ditions (including 1 ppm NO_2 and traces of nitric acic which BP was exposed to the gases in ambient photochen smog (ppm levels of NO_2, O_3, and peroxyacetyl nitrate). A exposure, the reaction products were separated and pur by thin layer chromatography and analyzed by mass s trometry. The products were then tested for mutagenic ac ty with *Salmonella typhimurium* strains TA1535, TA1 TA1538, TA98, and TA100, with and without the addi of 0.5 ml rat liver S9 mix as the metabolic activator. Re of the Ames reversion assay revealed that directly ac mutagenic nitro derivatives were readily formed from B perylene in stimulated atmospheres and that directly ac mutagens were formed from BP in photochemical smog. mation of direct mutagens by similar reactions on sar collection filters, in exhaust effluents, and in the atmosp is possible. (36 refs)

78-5569 **Cytologic Correlates of Chemical Carcinog in Respiratory Tracts of Dogs.** (Eng) M sumura, K. (Chiba Univ. Sch. Medicine, Inst. Pulmor Cancer Res., Chiba, Japan); Cohen, A. H.; Shors, E. C.; H field, J. R. *J Natl Cancer Inst* 61(5): 1209-1214; 1978.

Serial cytologic studies were made of 54 dogs during resp tory carcinogenesis induced by benzo(a)pyrene (BP) and N-methyl-N-nitrosourea (NMU). Dogs received submuc injections of either 45 mg BP coupled with ferric oxide mg NMU to total doses of 810 and 810-945 mg, respectiv Another group received 21 weekly submucosal injection 15 mg BP followed by 27 weekly doses of 10 NMU for a t of 315 mg BP and 270 mg NMU. Abnormal cells appea within 1 mo after the first carcinogen injection. In the e stage, BP induced changes primarily in the cytoplasm. Th changes consisted of increased size, basophilia, and vacu zation. NMU induced primarily nuclear enlargement and hanced the prominence of the nucleolus. After 6 mo, c exposed to BP demonstrated pleomorphism of the cytopl and nucleus, but cells exposed to NMU formed bizarre sp dle-shaped cells. Cells were generally more scattered fr one another following BP treatment than after NMU tr ment. When the mucosa was exposed to BP + NMU, cytologic features became those characteristic of lesions duced by NMU from the outset. These serial cytologic stu of bronchial brushings provided insights that repetitive bi sies did not, but biological significance of the observed ste typic patterns to cytologic morphogenesis is not clear. refs)

5570 **Ultrastructure of Early Stages in N-Diethylnitrosamine and Benzo(a)pyrene Induced Lung rcinogenesis.** (Eng) Reznik-Schuller, H. (Abteilung fur perimentelle Pathologie, Medizinische Hochschule Hanver, 3000 Hannover 61, W. Germany); Mohr, U. *In: Prevtion and Detection of Cancer. Proceedings of the Third International Symposium on Detection and Prevention of Cancer ld by the International Study Group for the Detection and evention of Cancer in New York, April 26 - May 1, 1976.* ernational Study Group for the Detection and Prevention Cancer. (New York, NY): Vol. 2(Part 1), 2404 pp.; 05-1318; 1978.

e early effects of N-diethylnitrosamine (DEN) and ben-(a)pyrene (BP) in the lungs of Syrian golden hamsters were amined by electron microscopy. Forty animals were injectsc with DEN (1/10 LD_{50}, 2x/wk), and 20 were given intracheal instillations of BP (0.63 mg/animal, 1x/wk). Anils were sacrificed at regular intervals up to 20 wk of atment. Following DEN treatment, nonciliated cells freently contained lamellated inclusion bodies in their cytosm, and proliferation of both nonciliated and APUD (ane precursor uptake and decarboxylase activity) cells was served. In addition, squamous metaplasias developed in the ar bronchi. None of these effects were observed after BP ministration. The earliest BP-induced alterations occurred er 3 wk in ciliated cells, and they were either a reduction the number of cilia per cell or a deformation of cilia. These erations occurred late in DEN treatment. Penetration of e basement membrane, with subsequent development of enomas, was induced by both carcinogens. These findings dicate that in bronchial epithelia, very early cellular reacns to carcinogen treatment vary according to the carcinon and its mode of administration but that the later steps e similar. (10 refs)

3-5571 **Effects of Exposure to Furfural Vapour in Hamsters Simultaneously Treated with Benzo[a]pyne or Diethylnitrosamine.** (Eng) Feron, V. J. (Central Inst. utrition and Food Res. TNO, Zeist, Netherlands); Kruysse, . *Toxicology* 11(2): 127-144; 1978.

rian golden hamsters were exposed to furfural vapor (0 or 50/400 ppm for 7 hr/day) 5 days/wk for 52 wk to study e effects of long-term repeated exposures. Some animals ere simultaneously given intratracheal benzo(a)pyrene (BP, 3.2 or 36.4 mg total) weekly for 52 wk or sc diethylnitrosaine (DENA, 2.1 μl total) every third wk for 52 wk. The udy was terminated after 81 wk. The animals' coats became llowish-brown during furfural treatment, and body wts deeased relative to control animals. The death rate was not fected by furfural or clearly influenced by BP or DENA. here were no significant differences in hematological or biochemical findings or organ-to-body-wt ratios between furfual-treated and control hamsters. Furfural exposure caused ritation of the nasal mucosa, atrophy and downward growth f sensory cells of the olfactory epithelium, degenerative changes in Bowman's glands, and the occurrence of cyst-like structures in the lamina propria beneath the olfactory epithelium. Furfural did not affect the tumorigenicity of BP or DENA. It is concluded that furfural is not a significant cofactor in respiratory tract carcinogenesis. (10 refs)

78-5572 **Relative Carcinogenic Effectiveness of Derivatives of Nitrosodiethylamine in Rats.** (Eng) Lijinsky, W. (Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21501); Taylor, H. W. *Cancer Res* 38(8): 2391-2394; 1978.

The carcinogenicity of five of nitrosodiethylamine derivatives, administered po to Sprague-Dawley rats, was compared with that of the parent compound. All were less potent than nitrosodiethylamine. When nitrosobis(2-methoxyethyl) amine and nitrosobis(2-ethoxyethyl)amine were administered at equimolar doses (0.68×10^{-3} M) in drinking water, there was a high incidence of liver tumors, but the animals survived longer than after nitrosodiethylamine treatment, which also induced esophageal tumors. Nitrosoiminodipropionitrile and nitrosobis(2,2-diethoxyethyl)amine failed to induce tumors at the same doses. Nitrosobis(2-chloroethyl)amine was administered in oil by gavage at a dose (1.15 mg 2x/wk) lower than that of nitrosodiethylamine, and produced a much weaker tumor response: 5/15 treated rats had forestomach papillomas and 1 had an olfactory adenocarcinoma. (17 refs)

78-5573 **Carcinogenesis of N-Nitrosodiethylamine (DENA) in Chickens and Domestic Cats.** (Eng) Schmahl, D. (Institut fur Toxikologie und Chemotherapie, Deutsches Krebsforschungszentrum, im Neuenheimer Feld 280, 6900 Heidelberg, W. Germany); Habs, M.; Ivankovic, S. *Int J Cancer* 22(5): 552-557; 1978.

The carcinogenicity of N-nitrosodiethylamine (DENA) was investigated in two new animal models, the chicken and cat, and reviewed in 16 other animal species. Six White Leghorn chickens were inoculated im 2x/wk with 10 mg/kg DENA for 50 wk (median total dose, 1,000 mg/kg) and five domestic short-haired cats were fed a 10% DENA soln in milk 5x/wk (daily dose, 1.5-2 mg/kg; median total dose, 870 mg/kg). All test animals showed severe toxic injury to the liver. In the chickens, median survival was 518 days. Three of the six chickens developed tumors: 1 developed multiple benign adenomas of the kidney; 1 a hepatocellular carcinoma and a pheochromocytoma of the adrenal gland; and 1 a hepatocellular carcinoma and an adenocarcinoma of the kidney. In the cats, median survival was 545 days. Three cats died with hepatocellular carcinomas; one of these animals also had multiple cholangiogenic adenomas and an early cholangiocellular carcinoma, and another showed peliosis hepatis and a cavernous hemangioma. DENA is carcinogenic in all species in which it has been tested adequately, with the liver proving

to be the main target organ. It is highly probable that DENA will act as a carcinogen in humans. (49 refs)

78-5574 **Enhancement by WY-14,643, A Hepatic Peroxisome Proliferator, of Diethylnitrosamine-Initiated Hepatic Tumorigenesis in the Rat.** (Eng) Reddy, J. K. (Dept. Pathology, Northwestern Univ. Medical Sch., 303 East Chicago Ave., Chicago, IL, 60611); Rao, M. S. *Br J Cancer* 38(4): 537-543; 1978.

The hepatic peroxisome proliferator (4-chloro-6-(2,3-xylidino)-2-2pyrimidylthio)acetic acid (WY-14,643) enhanced the development of liver tumors in male F-344 Charles River rats given diethylnitrosamine (DEN: 100 parts/10^6) in drinking water for 14 days. Beginning 1 wk after DEN treatment, rats in groups of 30 animals each were fed diets containing 0.1% WY-14,643 or 0.5% clofibrate (CFB) for 48 wk. Laparotomies at 22 wk revealed grossly visible liver nodules in only an occasional rat fed CFB, compared with approx 60% of rats fed WY-14,643. By 48 wk all 28 surviving Wy-14,643 treated rats had developed multiple tumors, 2-35 mm in diameter, involving all lobes. All tumors >10 mm were hepatocellular carcinomas; two rats also developed kidney adenomas. In the CFB group, 25/28 animals had liver tumors. The tumor incidence in this group was significantly greater than that (5/18) in rats receiving a control diet after DEN, but it was significantly less than that in the Wy-14,643 group. Although the enhancement of liver tumorigenesis by Wy-14,643 may be due to its hepatomegalic and peroxisome proliferative properties, the final mechanism remains to be elucidated. (33 refs)

78-5575 **The Influence of Diazepam and Thiouracil upon the Carcinogenic Effect of Diethylnitrosamine in Gerbils.** (Eng) Green, U. (Abteilung fur Experimentelle Pathologie, Medizinische Hochschule Hannover, Karl-Wiechert-Allee 9, D-3000 Hannover-Kleefeld, W. Germany); Ketkar, M. *Z Krebsforsch* 92(1): 55-62; 1978.

The influence of diazepam (DZP) and thiouracil (TU) on N-diethylnitrosamine (DEN)-induced carcinogenesis was examined in gerbils. One group of gerbils received DZP (10 mg intragastrically 1 x/wk for life) and, 30 min later, DEN (23 mg/kg sc 1 x/wk for life). Another group was fed TU daily (2,000 ppm in the diet) + DEN. Other groups received DEN, DZP, or TU alone. Animals receiving DZP + DEN or TU + DEN had significantly higher av survival times (53%-80% and 43%-90% higher, respectively) than gerbils receiving DEN alone. This longer av survival time resulted in a significantly higher total dosage of DEN. However, similarly high incidences of tumor (mainly adenocarcinomas), originating in the nasal cavities were seen in the DEN alone and combined treatment groups. Hepatic neoplasms were found as early as 15 wk after the start of treatment with DEN alone, but these tumors were first observed after 40 wk in the DZP + DEN animals and after 44 wk in the TU + D group. DEN alone selectively induced well-differenti cholangiocarcinomas, whereas cholangiomas were ma found in animals given the combined treatments. No tu were found in animals treated with DZP or TU alone. D has to be activated enzymatically to form its proximate a /or ultimate carcinogen. The results indicate that this me olism is inhibited in gerbils by the simultaneous adminis tion of DZP or TU. (13 refs)

78-5576 **Glucocorticoid Binding and Response in Liver and Diethylnitrosamine (DENA)-indu Hepatomas.** (Eng) Snart, R. S. (Dept. Zoology, The Un Sheffield, S10 2TN, England); Thorne, J. *J Steroid Bioch* 9(8): 709-715; 1978.

The binding of ^{3}H-dexamethasone (^{3}H-dex) in normal diethylnitrosamine (DENA)-treated rat liver was studi Wistar rats were given DENA (50 mg/ml) in their drink water beginning at age 6 wk. Liver preparations were tained from normal and DENA-treated rats at 4, 8, 12, 17 wk after the start of DENA treatment. The binding ^{3}H-dex to rat liver cytosol, plasma, and nuclei was de mined, as was the binding of the ^{3}H-dex-receptor comple DNA. There were no differences between normal rat liv and DENA-induced hepatomas with regard to glucoc ticoid binding to receptor proteins and translocation of receptor-steroid complex into the nucleus or the ability of t complex to bind to DNA. Tyrosine amino transferase (TA activity in rat livers was refractory to corticosterone and treatments, but following adrenalectomy, a highly signific response was observed. The DENA-induced hepatomas h slightly reduced levels of TAT activity, but this enzyme v stimulated significantly by corticosterone and very well dex. The plasma corticosterone concentrations DENA-treated rats were significantly lower than norm concentrations. It is suggested that the resulting feedback hibition due to unmetabolized glucocorticoid decrea ACTH release and seriously affects adrenal function. A creased steroid metabolism in DENA-treated rat livers co also account for the increased tissue sensitivity to the h mone. (16 refs)

78-5577 **Chemical Studies on Carcinogenic Nitro mines. 1. Hydrolysis of α-Acetoxynitrosamin** (Eng) Baldwin, J. E. (Dept. Chemistry, Massachusetts In Technology, Cambridge, MA, 02139); Scott, A.; Branz, S. Tannenbaum, S. R.; Green, L. *J Org Chem* 43(1 2427-2431; 1978.

Chemical reactions of the two structural isomers of α-aceto ymethylbenzylnitrosamine, one of which is a powerful ba terial mutagen whereas one is inactive, were studied. N cleophilic attack at the α carbon resulted in hydrolysis methanolysis, but attack at the carbonyl carbon by n-propy

e.g., yielded N-n-propylacetamide and the unstable α-
oxynitrosamine. The hydrolysis and methanolysis ap-
to occur via an SN1 reaction, involving a reso-
e-stabilized benzylnitrosimminium ion. The deacylation
imary amines was strongly activated by the nitrosamino
o, probably via an inductive effect, and it did not involve
lic intermediate. (12 refs)

578 **Oxidative Decarboxylation of Nitrosoamino Acids: A Synthetic Approach to Cyclic α-Ace-
itrosamines.** (Eng) Saavedra, J. E. (NCI Frederick Can-
Res. Center, Frederick, MD, 21501). *Tetrahedron Lett* 1923-1926; 1978.

minary studies of the one-step synthesis of α-acetoxyni-
pyrrolidine and α-acetoxynitrosopiperidine by oxidative
rboxylation of the corresponding nitrosoamino acids
lead tetraacetate are reported. Since α-acetoxynitrosa-
s may be direct-acting carcinogens, they should be treat-
ith caution. (14 refs)

579 **The Fragmentation Reaction of β-Hydroxyni-
trosamines: Possible Environmental and Bio-
nical Significance for Nitrosamine Carcinogenicity.**
g) Loeppky, R. N. (Dept. Chemistry, Univ. Mis-
i-Columbia, Columbia, MO); Christiansen, R. *IARC Sci* l (19): 117-126; 1978.

ability of β-hydroxynitrosamines (OH-NA's) to undergo
-catalyzed fragmentation (ie, retroaldol-type, cleavage
sformation) into an NA and a carbonyl product was de-
ined. Six OH-NA's were synthesized, and their behavior
ard strong base (3 M KOH) was examined. All six com-
nds underwent fragmentation, three with high reactivity,
e with low reactivity. The reverse reaction (aldol-type
densation) is prevented by the occurrence of Cannizaro
ldol-type condensation of the carbonyl product. This fact
account for the low reactivity of three of the OH-NA's,
he nature of their carbonyl products prevented or made
ifficult for them to enter into condensation reactions. It
ggested that fragmentation and condensation could oc-
while NA's are being isolated from substances such as
d products. Severe alkaline conditions should be avoided
he isolation and analysis of NA's from natural sources,
consideration must be given to the possibility that frag-
ntation may have occurred in past work. The fragmenta-
n may have a biochemical counterpart that is significant
the biochemical mechanism of NA carcinogenesis. (17
)

-5580 **Effect of Dose on the Carcinogenic Activity of Orally Administered N-Bis(2-hydroxy-
opyl)nitrosoamine in Rat.** (Eng) Konishi, Y. (Dept. Oncological Pathology, Cancer Center, Nara Medical Univ., 840 Shijo-cho, Kashihara 634 Japan); Kondo, H.; Ikeda, T.; Kawabata, A.; Shoji, Y.; Denda, A. *Gann* 69(4): 573-577; 1978.

Male Wistar rats were given 100 ppm N-bis(2-hydroxypropyl)nitrosamine (DHPN) in drinking water and sacrificed at 25 wk (Group 1) or 52 wk (Group 2), or they were given 500 ppm DHPN and sacrificed at 25 wk (Group 3) or 29-39 wk (Group 4). Two lung adenomas occurred among 12 Group I animals. Three hepatocellular carcinomas, 1 liver hemangioma, 3 thyroid adenomas, and 6 lung adenomas, 3 adenocarcinomas, and 1 squamous cell carcinoma of the lungs were found among 10 Group 2 rats. All 12 Group 3 rats developed lung adenomas; in addition, 2 developed a lung adenocarcinoma and 4, a squamous cell carcinoma. Nine surviving animals in Group 4 developed numerous tumors in various tissues, including 22 lung tumors, 7 liver tumors, 1 thyroid tumor, 5 esophageal tumors, 2 kidney tumors, and 1 bladder tumor. Therefore, lung tissue was affected most severely by this carcinogen; the fact that no pancreatic tumors were identified is interesting, because DHPN is a potent pancreatic carcinogen in Syrian golden hamsters. (20 refs)

78-5581 **A Cell Line Derived from BBN [N-Butyl-N-(4-hydroxybutyl)nitrosamine]-induced Rat Bladder Cancer: Establishment and Scanning Electron Microscopic Cell Surface Characteristics.** (Eng) Nishi, M. (Dept. Urology, Okayama Univ. Medical Sch., Okayama 700, Japan). *Acta Med Okayama* 32(3): 181-205; 1978.

The surface structure of bladder cancer cells was studied by scanning electron microscopy using synchronized cultures of lines cloned from rat bladder cancers induced by N-butyl-N-(4-hydroxybutyl)nitrosamine. Tumors were induced in male Wistar rats raised with drinking water containing 0.05% of the carcinogen. After several subcultures, the cells exhibited loss of contact inhibition and marked piling-up behavior. Because single-cell cloning was difficult, colonies of cells were cloned. The population doubling time of the parent strain and the clones was approx 30 hr. The chromosome mode was in the triploid to tetraploid range. Plating efficiency was $<20\%$. Backtransplantation of 5×10^6 cells ip into newborn rats produced tumors in all cases. Histopathologically, some parts of these tumors resembled primary transitional cell carcinoma. However, the major tumor cell groups showed marked keratinization and resembled squamous cell carcinoma. Compared with normal bladder mucosa cells, the nucleus cytoplasm ratio and the number of nucleoli, free ribosomes, and intracytoplasmic microfibrils were increased. The ultrastructure was characterized by a profuse arrangement of microvilli, parts of which were joined to desmosomes. During mitosis, the cells became large and globular; the microvilli decreased in height and were gathered profusely over the entire surface. Cells in G_1-S developed lamellipodia and pseudopodia-like cytoplasmic processes and were polygonal. Microvilli were present in the central part

containing the nucleus, but they were somewhat decreased in number and increased in height. (37 refs)

78-5582 **Inhibitory Effect of 13-*cis*-Retinoic Acid on Urinary Bladder Carcinogenesis Induced in C57BL/6 Mice by N-Butyl-N-(4-hydroxybutyl)nitrosamine.** (Eng) Becci, P. J. (Life Sciences Div., IIT Res. Inst., Chicago, IL, 60616); Thompson, H. J.; Grubbs, C. J.; Squire, R. A.; Brown, C. C.; Sporn, M. B.; Moon, R. C. *Cancer Res* 38(12): 4463-4466; 1978.

The effect of 13-*cis*-retinoic acid (CRA) on the induction of highly invasive urinary bladder carcinoma by N-butyl-N-(4-hydroxybutyl)nitrosamine (OH-BBN) was studied in male C57BL/6 mice. Tumors were induced by gastric intubation of OH-BBN in doses of 7.5 or 10.0 mg 2 x/wk for 6 or 7 wk, respectively. Seven days after the last carcinogen intubation, mice were fed a placebo diet or a diet supplemented with 200 mg/kg CRA. Autopsies performed 6 mo following the first carcinogen treatment revealed highly invasive squamous and transitional cell carcinomas of the urothelium. In most cases, tumor cells had penetrated the bladder muscle wall. The CRA diets reduced the incidence of carcinomas and noninvasive papillomas, as well as the extent of neoplastic development in the bladder, induced by either dose of OH-BBN. At the lower dose of OH-BBN, CRA prevented the appearance of both squamous and transitional cell carcinoma, with a reduction of incidence from 33% to 0%. These findings suggest that CRA can reduce both the severity and the incidence of chemically induced urinary bladder carcinomas. (8 refs)

78-5583 **Effect of Protease Inhibitors in Mice Treated with the Hepatocarcinogen, Hexachlorocyclohexane (α-Isomer) and the Bladder Carcinogen, N-Butyl-N-(4-hydroxybutyl)nitrosamine.** (Eng) Arai, H. (First Dept. Pathology, Nagoya City Univ. Medical Sch., 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467, Japan); Shirai, T.; Hananouchi, M.; Hirose, M.; Murasaki, G.; Ito, N. *Gann* 69(4): 593-595; 1978.

One of the protease inhibitors pepstatin (PS), leupeptin (LP), and antipain (AP) (each, 0.1% in diet) were administered to male DDY mice that had been fed the α-isomer of 1,2,3,4,5,6-hexachlorocyclohexane (α-BHC) (500 ppm for 24 wk) or to male ICR mice that had been given N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN) (0.05% of drinking water for 8 wk). Animals treated with LP + α-BHC experienced a significant increase in hepatic nodular hyperplasia (HNH: 5/12 vs 1/13 in α-BHC-only mice), and they developed the only α-BHC-induced hepatoma. Groups given α-BHC and the other two protease inhibitors did not show any significant differences in HNH from the α-BHC-only group. In all BBN + protease inhibitor groups, the urinary bladder changes were similar to those of the BBN-only group: 7 simple hyperplasias, 4 papillary or nodular hyperpla 1 papilloma, 1 cancer, and no hemangiomas among 13 mals. Hemangiomas did occur in the BBN + PS (3/10) BBN + LP (1/16) groups. Treatment with protease inhil alone in both experiments did not produce any char Thus, it appears that LP enhances the induction of NNI α-BHC. (10 refs)

78-5584 **Cell Kinetics of Mouse Urinary Bladder thelium. VII. Changes in Proliferation and clear DNA Content after Repeated Doses of Dibutylnitr mine.** (Eng) Farsund, T. (Haukeland Sykehus, N- Bergen, Norway); Iversen, O. H. *Virchows Arch [Cell Pa* 27(2): 119-135; 1978.

The effect of repeated sc injections of dibutylnitrosa (DBN; 0.01 ml in 0.2 ml propylene glycol) on the cell kin of the urinary bladder epithelium was investigated in hairless hr/hr Oslo strain mice. The animals were div into two groups: Group 1 received the injections three t weekly for 3 mo; Group 2 received the injections once a for 6 mo. A high mortality (24/72) was noted in Grou no Group 2 animals died during the observation pe DNA synthesis in the tetraploid cells of both groups inhibited early in the experimental period; this inhibition followed by a disappearance of the octoploid and, finally tetraploid cells. In the diploid cells, however, the lab index, the proportion of cells in the S phase, and the mi rate increased. Thus, repeated DBN injections led to a hy plasia of the diploid cells due to a high rate of diploid proliferation and a block in the mechanism of repeated I synthesis. Malignant transformation was noted in Gro after 5-6 mo. These changes in urothelial cell turnover qualitatively similar to, but more pronounced, than thos duced by injections of cyclophosphamide or propylene gl It is suggested that the strong and early effect of DBI diploid, basal cell DNA synthesis and on the mechanis repeated DNA synthesis in the bladder mucosa is linke the carcinogenicity of DBN. (22 refs)

78-5585 **Ultrastructure of Nitrosoheptamethyl mine-induced Lung Tumors in European H sters.** (Eng) Reznik-Schuller, H. (Chemical Carcinoge Section, Frederick Cancer Res. Center, P. O. Box B, Fr rick, MD, 21501). *Am J Pathol* 93(1): 45-52; 1978.

The ultrastructure of nitrosoheptamethyleneir (NHMI)-induced lung tumors (LT) in European ham (EH) is described and compared with that of tumors ind in the same species and in Syrian golden hamsters by c nitrosamines. Ten male EH were given weekly sc injec of 66 mg/kg NHMI until they showed clinical signs of All animals developed nasal cavity tumors and multiple Light microscopically, the LT showed an adenomatou mixed (areas with adenoid and poorly keratinized squan

ferentiation) pattern. Electron microscopically, the nomatous neoplasms (adenomas and adenocarcinomas) the areas of adenoid differentiation in the mixed tumors sisted predominantly of Clara cells and of cells with ellated inclusion bodies and various amounts of smooth doplasmic reticulum in their cytoplasm. Areas of squa-us differentiation contained cells in which a gradual loss dense-cored granules coincided with an increasing occur-ce of cytoplasmic filaments. These LT were similar to se induced in EH by N-dibutylnitrosamine and to those uced in Syrian golden hamsters by diethylnitrosamine, utylnitrosamine, and nitrosomorpholine. (20 refs)

5586 **Autoradiography and Organ Distribution of N-Methyl-N-nitrosobenzylamine in Rats.** (Eng) uka, T. (Serology Div., Natl. Cancer Center Res. Inst., ukiji, 5-1-1, Chuo-ku, Tokyo 104, Japan); Ichimura, S.; wachi, T. *Gann* 69(4): 487-492; 1978.

e mechanism of esophageal carcinoma induction by methyl-N-nitrosobenzylamine (MNBA) or by N-methyl-nzylamine (MBA) + sodium nitrite, which form MNBA stomach acid, was studied in male Donryu rats. The distri-tion of labeled MNBA was determined by autoradiogra-y. One group of rats was given a soln of 120-150 mg/kg BA + 77-100 mg/kg $NaNO_3$ intragastrically. Four groups re given 83 mg/kg MNBA ip, im, sc, and intragastrically, spectively. All groups of rats developed esophageal ulcers thin 1-4 days. Those produced by MNBA were deeper and ore severe than those produced by MBA + $NaNO_3$. hole-body autoradiography showed that the radioactive take was high in the esophagus and liver of rats inoculated with labeled MNBA; the radioactivity persisted in these sues at 24 hr. Incorporation of label was higher in the ophagus than in any other part of the gastrointestinal tract. icroautoradiography displayed a concentration of silver ains in both esophagus and liver, particularly in the mucous embrane of the esophagus. Thus, MNBA has a specific af-nity for the esophagus, eventually resulting in the develop-ent of carcinoma. (10 refs)

3-5587 **Nitrosobenzylmethylamine, Zinc Deficiency and Oesophageal Cancer.** (Eng) Fong, L. Y. Massachusetts Inst. Technology, Cambridge, MA); New-erne, P. M. *IARC Sci Publ* (19): 503-513; 1978.

he effects of zinc deficiency on esophageal cancer induction y nitrosobenzylmethylamine (NBMA) were investigated by eding weanling Charles River CD strain male rats a basal n-deficient (Zn-) diet containing 7 ppm Zn (30 rats) or a ontrol diet containing 60 ppm Zn ad libitum (20 rats: ad libum-fed controls). After 12 wk (at 15 wk of age), NBMA mg/kg 2 x/wk) was administered by intragastric intuba-on for 12 wk. In a second experiment, 40 rats received a n- diet for 4 wk and 40 rats served as pair-fed controls. After 4 wk (at 7 wk of age), NBMA was administered as above. Zn determinations were made in the serum, hair, esophagus, testes, liver, and kidneys; Zn- rats were retarded in growth compared with ad libitum-fed controls. Furthermore, pair-fed controls, although of comparable size, did not show the hair deficiencies and dermal lesions common in Zn- rats. In the first experiment, 43% of the Zn- rats developed esophageal carcinoma vs 15% of the ad libitum-fed controls. In the second experiment, 83% and 33% of the Zn- animals (sacrificed at 58 and 93 wk, respectively) developed esophageal carcinoma vs 0% of the pair-fed controls. Tumor induction time was shorter in all Zn- rats. Zn levels in serum, hair, testis, and esophagus were depressed in all Zn- animals, although liver levels were unchanged in all groups. It is suggested that Zn deficiency enhances the induction of esophageal cancer in the rat. (17 refs)

78-5588 **Mode of Mutagenic Action of Methylnitrosocyanamide, a Potent Carcinogen.** (Eng) Hidaka, K. (Cancer Res. Inst., Faculty Medicine, Kyushu Univ., Fukuoka 812, Japan); Ishizawa, M.; Otsuji, N.; Endo, H. *Cancer Res* 38(12): 4630-4633; 1978.

To study the mode of mutagenic action of methylnitrosocyanamide (MNC), N-methyl-N′-nitro-N-nitrosoguanidine (MNNG), and N-methyl-N-nitrosourea (MNU), revertants induced by treatment of a strain of *Escherichia coli* carrying nonsense mutations in the tryptophan (*trp*) and alkaline phosphatase (*phoA*) genes were analyzed. Trp+ revertants were purified and classified into seven categories based on their ability to support the growth of particular nonsense mutants of phage λ and on their content of alkaline phosphatase. About 90% of the trp+ revertants induced by MNC were due to mutations in suppressor genes, and 85% of the suppressor mutations occurred in the suppressor gene *supE*. Intragenic reversion cannot occur by a GC(to)AT base-substitution mutation, whereas this is the obligate mode of mutation in gene *supE*. It is concluded that MNC preferentially induces GC(to)AT transition mutations but that other base-substitution mutations are also induced at about 10% of this frequency. NMU and, particularly, MNNG, also preferentially induce GC(to)AT transition mutations. (25 refs)

78-5589 **Mutagenicity of N-Nitrosopiperazine Derivatives in *Salmonella typhimurium*.** (Eng) Rao, T. K. (Biology Div., Oak Ridge Natl. Lab., Post Office Box Y, Oak Ridge, TN, 37830); Young, J. A.; Lijinsky, W.; Epler, J. L. *Gen Pharmacol* 57(2): 127-134; 1978.

A series of nitrosopiperazine derivatives was tested for mutagenicity in the *Salmonella typhimurium*/microsomal activation system, using strains TA1535, TA100, TA1537, TA158, and TA98. Compounds tested were N-nitrosopiperazine, N-methyl-N-nitrosopiperazine, dinitrosopiperazine, 2-methyldinitrosopiperazine, 2,5-dimethyldinitrosopipera-

zine, 2,6-dimethyldinitrosopiperazine, and 2,3,5,6-tetramethyldinitrosopiperazine, dinitrosohomopiperazine, and 4-benzoyl-3,5-dimethylnitrosopiperazine. These compounds required metabolic activation; max activity was obtained with phenobarbital-induced rat liver microsome enzymes. There was a good correlation between a positive effect in the mutation assay and the known carcinogenic potency of the compound. These results demonstrate the predictive value of an in vitro activation system using *S. typhimurium* to detect carcinogenic compounds as mutagens. (14 refs)

78-5590 **Metabolism of Acyclic and Cyclic N-Nitrosamines by Cultured Human Colon.** (Eng) Autrup, H. (Human Tissue Studies Section, Experimental Pathology Branch, Carcinogenesis Program, NCI, Bethesda, MD, 20014); Harris, C. C.; Trump, B. F. *Proc Soc Exp Biol Med* 159(1): 111-115; 1978.

The metabolism of several acyclic and cyclic N-nitrosamines was studied in human colon mucosa cultures derived from 11 patients, 7 with and 4 without cancer of the colon. Nitrosamine metabolism was measured by $^{14}C\text{-}CO_2$ formation and reacton of the activated moieties with cellular DNA and protein. Dimethylnitrosamine (DMN) and N-nitrosopyrrolidine (NPy) were metabolized by explants from all patients studied. Diethylnitrosamine (DEN) was metabolized by explants from two patients, N′,N-dinitrosopiperazine (DNP) by five, and N-nitrosopiperidine by one. No $^{14}C\text{-}CO_2$ was formed from N-nitrosonornicotine. A positive correlation between binding of DMN to DNA and CO_2 formation was observed. DMN alkylated DNA in both the 0-6 and N-7 positions of guanine. However, most of the radioactivity was associated with an acid-labile compound. High binding levels of DNP to protein without concomitant binding to DNA were detected. Interindividual variation in both binding level to DNA and ability to metabolize the different N-nitrosamines was observed. These findings suggest that the colon should be considered one of the organs that are likely to be susceptible to the carcinogenic action of N-nitrosamines. (36 refs)

78-5591 **Demonstration of the Presence of Nitrosamine in Human Urine: Preliminary Observations on a Possible Etiology for Bladder Cancer in Association with Chronic Urinary Tract Infection.** (Eng) Hicks, R. M. (Sch. Pathology, Middlesex Hosp. Medical Sch., London, England); Gough, T. A.; Walters, C. L. *IARC Sci Publ* (19): 465-475; 1978.

In view of the ability of nitrate-reducing bacteria to synthesize N-nitrosodimethylamine (DMNA) from precursors, a study was undertaken to determine whether human urine contains elevated levels of nitrosamines (NA's) during bacterial cystitis of the bladder and whether there is any connection between these elevated levels and subsequent bladder cancer. Urine was collected from hemi- and paraplegic British men, British bladder cancer patients, Egyptians with
der cancer and superimposed bilharzial bladder di
(BBD), Egyptians with uncomplicated BBD, British
trols, and Egyptian controls. Total NA content was
mined by optical density measurements, volatile NA co
by gas chromatography-mass spectrometry. NA's were
sent in 3/10 paraplegics, all three with active bacterial
tis, and in the single British cancer patient with active ba
al infection. Elevated levels of urinary NA's were
detected in 4/15 Egyptian bladder cancer patients with
Their urine was not examined for bacteria, but infecti
these patients is commonplace. Six of 10 Egyptians wit
complicated BBD, 7 of whom had infected urine, sh
traces of NA's, but these levels were much lower than
in the cancer patients with BBD. The NA levels in Egy
bladder cancer patients were much higher than those
in the British patients, which suggests that there is an
unidentified factor in the urine of the former that pro
nitrosation. The only NA positively identified was DM
but strong evidence was obtained that other extractabl
not yet identified, NA's were also present. The results
that NA's were only in urine in which bacterial infectio
established or commonplace. It is suggested that bac
enzymes in infected patients reduce nitrate to nitrite,
can then nitrosate available precursors to potentially ca
genic NA's. (12 refs)

78-5592 **Repeated Partial Hepatectomy as a Prom
Stimulus for Carcinogenic Response of Li
Nitrosamines in Rats.** (Eng) Pound, A. W. (Dept. Path
Univ. Queensland, Brisbane, Australia); McGuire, L.
J Cancer 37(4): 585-594; 1978.

The effect of partial hepatectomy (PH) on the tumori
response of nitrosamine-treated male Sprague-Dawle
was investigated. Rats were given a two-thirds PH foll
by 100 mg/kg diethylnitrosamine (DEN), 20 mg/kg
thylnitrosamine, or 30 mg/kg ethylmethylnitrosamin
Compared with control rats (laparotomy alone plu
trosamines), this treatment increased both the number
er tumors and the number of focal proliferations. In a s
experiment, rats (Group I) were given a hepatonecrotic
of 1.0 mg/kg CCl_4 followed 24 hr later by a dose o
mg/kg DEN. Five, 10, and 15 wk later, these rats unde
three PH's. Three additional groups received CCl_4 +
the three PH's, or no treatment, respectively. The num
tumors in surviving animals was greatest in Group I rat
this result was not significant. The yields of focal pro
tions and cell foci could not be compared because of var
in areas of the liver scanned. The incidence of focal pro
tions was significantly greater in Group I animals foll
the second PH (at 15-20 wk), but the increase found
necropsy specimens (at 52 wk) was not statistically s
cant. If the single dose of DEN is regarded as an init
agent, the stimulus of repeated PH appears to act as
moting agent for hepatocarcinogenesis. (35 refs)

-5593 **Microsome-mediated Mutagenesis of a Chinese Hamster Cell Line by Various Chemicals eeting Abstract).** (Eng) Drevon, C. (International Agency s. Cancer, 150 cours Albert Thomas, 69008 Lyon, France); iroki, T.; Montesano, R. *Mutat Res* 53(2): 181-182; 1978.) refs)

3-5594 **A Comparison of Ascorbic Acid Excretion with Other Indicators of Nitrosamine Hepatotoxici-** . (Eng) Nishie, K. (Richard B. Russell Agricultural Res. enter, Science and Education Administration, U.S. Dept. griculture, Athens, GA, 30604). *Res Commun Chem Pathol harmacol* 20(3): 549-557; 1978.

Sprague-Dawley rats given single or multiple doses of four oncarcinogenic and seven carcinogenic nitrosamines (NA: arious doses in 0.5-1.0 ml olive oil/kg body wt, po), changes urinary ascorbic acid output were not indicative of NA arcinogenicity or acute hepatotoxicity. Histologic examina- on of the liver with glycogen staining was the most sensitive st of the acute effects of the NA carcinogens. The pentobar- ital-induced sleeping time test was intermediate, and the GOT test was the least sensitive. (12 refs)

8-5595 **Diffusion of Nitrosamines Through Protective Gloves.** (Eng) Gough, T. A. (Lab. Governent Chemist, London, England); Webb, K. S.; Mc- hail, M. F. *IARC Sci Publ* (19): 531-534; 1978.

The protection afforded by rubber and polyvinyl chloride loves against N-nitrosodimethylamine (DMNA), N-nitrosodiethylamine (DENA), N-nitrosodipropylamine NDPA), N-nitrosodibutylamine (NDBA), N-nitrosopiperidine (NPIP), and N-nitrosopyrrolidine (NPYR) was evaluated. The gloves were turned inside out, and 1 ml of a 10 μl/liter nitrosamine soln was placed in each of the four fingers. The outer faces of the fingers were washed every 10 min, and the washings were evaluated for nitrosamines by gas chromatography-mass spectrometry. In another experiment, the rubber in the gloves themselves were analyzed for nitrosamines, but none were found. For both glove types, NPYR permeated the fingers most rapidly, especially within the first 30 min, and to the greatest extent. Rubber gloves allowed diffusion in the following hierarchy: NPYR > NIPP > DENA > DMNA > NDPA > NDBA. After 2 hr, approx 57% of NRYR and 2.5% of NDBA had diffused through the gloves. Polyvinyl chloride gloves allowed diffusion in the following order: NPYR > NDPA > NPIP > DENA > DMNA. After 1 hr, approx 45% NPYR and 10% of DMNA had diffused though the gloves. It is concluded that the use of gloves does not give adequate protection from nitrosamine contamination of the hands. (3 refs)

78-5596 **The Permeability of Laboratory Gloves to Selected Nitrosamines.** (Eng) Sansone, E. B. (Frederick Cancer Res. Center, Frederick, MD); Tewari, Y. B. *IARC Sci Publ* (19): 517-529; 1978.

The permeability of five varieties of laboratory gloves to 0.136 to M solns of N-nitrosodimethylamine, N-nitrosodiethylamine, N-nitrosoethylmethylamine, N-nitrosobutylmethylamine, and N-nitrosodipropylamine, N-nitrosodiisopropylamine, and N-nitrosodibutylamine in acetone, dichloromethane, ethanol, and water was determined. Disks cut from gloves made of natural rubber, polyvinyl chloride, nitrite, neoprene, and a neoprene + natural rubber mixture were used to partition a permeability apparatus into two compartments that contained the permeant soln and water, respectively. Samples were withdrawn from the water side after 0.5, 1, 2, 4, 6, and 8 hr and analyzed for nitrosamine (NA's). In nearly all cases, readily measurable amounts of NA's penetrated glove materials within 0.5 hr. In general, penetration of NA's decreased with increasing mol wt in acetone, dichloromethane, and ethanol, whereas with water as solvent, NA's penetrated more readily as their mol wt increased. The results indicate that gloves should not be assumed to provide full protection, they should be discarded immediately following overt contamination, and they should not be reused. (14 refs)

78-5597 **Limitations to the Protective Effect of Rubber Gloves for Handling Nitrosamines.** (Eng) Walker, E. A. (International Agency Res. Cancer, Lyon, France); Castegnaro, M.; Garren, L.; Pignatelli, B. *IARC Sci Publ* (19): 535-543; 1978.

The rate of diffusion of N-nitrosodimethylamine (DMNA) and N-nitrosodiethylamine (DENA) through various types of rubber gloves was investigated. When a glove was filled with methylene chloride and suspended in a beaker containing an equal volume of methylene chloride soln containing 10 mg/liter each of DMNA and DENA, about 25% of both nitrosamines diffused through in 15 min. When saline was substituted on the inside of the barrier to simulate human perspiration, 10% of DMNA diffused through in 15 min. Slightly lesser values were determined for DENA. The thicker household gloves tested actually provided less protection than surgical gloves, possibly because of the properties of the materials constituting the two types of gloves. DMNA showed a tendency to concentrate in the rubber of surgical gloves and then equilibrate with the saline phase. The diffusion of other nitrosamines across a surgical glove barrier from methylene chloride to saline was also investigated, and after 20 min the relative hierarchy of diffusion was DMNA > N-nitrosopyrrolidine > DENA > N-nitrosopiperidine > N-nitrosomethylpentylamine > N-nitrosodipropylamine > N-nitrosodibutylamine. A double layer of surgical gloves successfully reduced exposure. Better protection was afforded by dusting the inner pair with talc. However, max protection

was afforded by smearing the inner pair with oil-resistant barrier cream, with only 2.9% of DMNA diffusing through the material after 30 min of exposure. (no refs)

78-5598 **Carcinogenesis by Nitroso Derivatives of Methylcarbamate Insecticides and Other Nitrosamides in Rats and Mice.** (Eng) Lijinsky, W. (Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD); Schmahl, D. *IARC Sci Publ* (19): 495-501; 1978.

Nitroso derivatives of methylcarbamide insecticides and other common nitrosamines were tested for carcinogenicity and mutagenicity by feeding and topical application to female BD rats. Animals were fed (by gavage) specified amounts of each derivative or nitroso-N-methylphenylcarbamate (NMPC) dissolved in corn oil 1 x/wk, or they had a 0.02 M soln of each nitroso compound in acetone painted on a shaved interscapular region 2 x/wk. All six nitrosated methylcarbamide insecticides and NMPC gave rise to forestomach tumors. Of 32 animals tested in each group, the numbers of tumor-bearers for each compound were: nitrosocarbaryl, 19; nitrosobaygon, 15; nitrosocarbofuran, 12; nitrosobux-ten, 11; NMPC, 11; nitrosolandrin, 9; and nitrosomethomyl, 4. Most of the tumors (63) were papillomas; the remainder (30) were carcinomas. Nitrosobaygon and nitrosocarbofuran each produced the greatest number of carcinomas (7). In skin-painting tests, N-methyl-N′-nitro-N-nitrosoguanidine produced 16 tumors, methyl-(d_3)-nitrosonitroguanidine 11, ethylnitrosonitro-guanidine, 8, methylnitrosourea 3, and methyl-(d_3)-nitrosourea 1. None of the other nitroso compounds gave rise to more than one tumor per group of 20 animals, an unexpected finding since approx 0.8 millimole/kg of each compound was applied. (11 refs)

78-5599 **Distribution of 7-Methylguanine and of Replication Sites in the Different Kinetic Classes of DNA from Rats Treated with Dimethylnitrosamine.** (Eng) Galbraith, A. I. (Paterson Labs., Christie Hosp. and Holt Radium Inst., Manchester M20 9BX, England); Chapleo, M. R.; Itzhaki, R. F. *Nucleic Acids Res* 5(9): 3357-3364; 1978.

Examination of the radioactivity level in the families of repetitive and unique sequences of DNA, after treatment of male Wistar rats with ^{14}C-dimethylnitrosamine (DMN) showed that the distribution of 7-methylguanine was random. Examination of the distribution of newly synthesized DNA after treatment of rats with DMN + ^{3}H-thymidine indicated that there is no difference in the extent of synthesis between the two kinetic classes. (28 refs)

78-5600 **Formation and Subsequent Removal of O⁶-Methylguanine from Deoxyribonucleic Acid in Rat Liver and Kidney after Small Doses of Dimethylnitrosam**
(Eng) Pegg, A. E. (Dept. Physiology, Milton S. Hers Medical Center, 500 University Drive, Hershey, PA, 170 Hui, G. *Biochem J* 173(3): 739-748; 1978.

The amounts of 7-methylguanine (7-MG) and O⁶-methyl nine (OMG) present in rat liver and kidney DN and 24 hr after female Sprague-Dawley rats v administered low doses of dimethylnitrosamine (DI were measured. Less than 15% of the expected amo of OMG (on the basis of 7-MG found) was presen liver DNA within 4 hr after ip doses of ⩽0.25 mg within 24 hr after doses of ⩽1 mg/kg, > 85% of expected amount of OMG was removed. Rem was max for DMN doses of 0.25-0.5 mg/kg; howe the reaction did not appear to be saturated even at the hig dose tested (20 mg/kg). Alkylation of kidney DNA after 1 μg/kg DMN ip occurred at about one-tenth the exten alkylation of liver DNA. Removal of OMG from kid DNA was slower than that from the liver. The alkylatio kidney DNA was much less after po administration of th doses than after ip administration, representing only 1%- of that found in the liver. Alkylation of liver and kidney D was readily detectable when measured 24 hr after the fi injection in rats that received daily injections of 1 μg ^{3}H-DMN for 2 or 3 wk. After 3 wk, OMG levels in liver D were about 1% of the 7-MG levels. The amount of 7-MG liver DNA was 10 times that in kidney DNA, but liver OM levels were only twice those in the kdiney. Extracts able catalyze the removal of OMG from alkylated DNA in v were isolated from liver and kidney. These extracts did lead to the loss of 7-MG from DNA. Although OMG-removal system may protect against carcinogenesis DMN and may be responsible for lowering the carcinoge risk from daily doses of 5-0.5 mg/kg by more than the sim factor between the doses, its existence does not imply t there is necessarily a threshold dose at which no tumors all would be expected. The findings that there is little react with the kidney after low po doses of DMN may explain w only liver tumors and not renal tumors are produced by p longed feeding of low DMN doses. (70 refs)

78-5601 **Effect of Pretreatment with Other Dialky trosamines on Excision from Hepatic DNA O⁶-Methylguanine Produced by Dimethylnitrosamine.** (E Pegg, A. E. (Dept. Physiology, Milton S. Hershey Medi Center, 500 Univ. Drive, Hershey, PA, 17033). *Chem I Interact* 22(1): 109-116; 1978.

The effect of pretreatment of rats with higher dialkylnitro mines (DAN's) on the amount of O⁶-methylguanine (OM found in hepatic DNA after administration of 10 μg/ ^{3}H-dimethylnitrosamine (DMN) were determined. Fem Sprague-Dawley rats were inoculated ip with DAN and, hr later, with DMN, and they were sacrificed 4 or 24 hr a the latter inoculation. Pretreatment with diethylnitrosam (DEN: 200 mg/kg) or dipropylnitrosamine (240 mg/kg) creased the amount of labeled OMG in liver DNA 4 and

after injection of DMN. Dibutylnitrosamine (600 mg/kg) d a similar though smaller effect at 4 hr, but the effect had rn off by 24 hr. These pretreatments did not effect ıethylguanine levels in the DNA, showing that metabolic ıversion of DMN into a methylating agent was not altered. reases in OMG levels must be due to interference with the s of this product from the DNA. Since the efficiency of ıoval of OMG from rat liver DNA has been shown to be atly reduced by increasing the dose of DMN, the most obable explanation of the reduced rate of excision following ministration of other DAN is that they also produce al-ed bases in the DNA similar to OMG and thus slow the e of repair. This hypothesis was supported by other experi-nts, which showed that 24 hr after administration of DEN, amount of O^6-ethylguanine in hepatic DNA was approx ual to the amount of OMG found after injection of DMN d that the rate of loss of the two guanines from the DNA s comparable; ie, both are removed by the same process. is method used here may be of value for determining ether cyclic nitrosamines produce similar products. The sults suggest that different nitrosamines might have addi-e effects in prolonging damage to DNA, a phenomenon at could be important in carcinogenesis. (30 refs)

-5602 **Effects of Dimethylnitrosamine on Induction of Cholangiocarcinoma in *Opisthorchis viverrini*-fected Syrian Golden Hamsters.** (Eng) Thamavit, W.)ept. Pathobiology, Faculty Science, Mahidol Univ., Rama I Road, Bangkok 4, Thailand); Bhamarapravati, N.; Sahap-ng, S.; Vajrasthira, S.; Angsubhakorn, S. *Cancer Res* (12): 4634-4639; 1978.

teractions between nitroso compounds and the presence of ver fluke (*Opisthorchis viverrini*) infections were studied in rian hamsters, in order to determine whether the concomi-nt occurrence of the endemic parasitic disease and cholan-ocarcinoma in northeastern Thailand could be related to e presence of nitrosating agents, nitrosatable substances, d nitrosamine compounds commonly present in foods in is region. All 18 animals that received dimethylnitrosamine MN, 0.0025%) in the drinking water for 10 wk, beginning wk after they were infected with metacercariae, developed olangiocarcinoma and cholangiofibrosis. The tumor was ot observed in controls receiving either DMN or parasites one, although cholangiofibrosis was found in some animals eated with DMN alone. It is postulated that the cholangi-carcinomas arose because the DMN exerted a carcinogenic ffect on the altered proliferating epithelial cells of bile ducts at had been stimulated by the parasite. These findings sug-est that the combination of DMN ingestion and liver fluke festation may play an important role in the carcinogenesis f intrahepatic duct neoplasms in humans. (28 refs)

78-5603 **Mechanism of Dimethylnitrosamine Metabolism and Activation in Rats.** (Eng) Godoy, H. M. (Laboratorio de Quimica Biotoxicologica, CITEFA, Zufriategui y Varela, Villa Martelli, Buenos Aires, Argentina); Diaz Gomez, M. I.; Castro, J. A. *J Natl Cancer Inst* 61(5): 1285-1289; 1978.

The effect of inducers and inhibitors of hepatic microsomal metabolism on dimethylnitrosamine (DMN) metabolism and activation was studied in Sprague-Dawley rat liver preparations. DMN was metabolized in liver slices to CO_2, and reactive metabolites were formed that bound to nucleic acids. SKF 525-A [2-(diethylamino)ethyl-2,2-diphenylvalerate hydrochloride: 0.5-2 mM] inhibited CO_2 production by 27.2%-92.9% and binding by 46%-91.4%. In liver slices from rats pretreated with phenobarbital sodium (PB) for 3 days, CO_2 production was 30.8% of control values, but covalent binding was only slightly altered. In liver slices from animals pretreated with $CoCl_2$, the metabolism of CO_2 was 32.4% of control values and binding was 60% of control values. An NADPH-dependent, heat-sensitive, DMN-activation process leading to reactive metabolites that bound covalently to proteins was also observed in the microsomes and 9,000 x *g* (qK) supernatants but not in the 100,000 x *g* (100K) supernatants. Treatment with 1 mM SKF 525-A strongly inhibited the activation process in microsomes but only slightly inhibited this process in the 9K supernatants. Microsomes or 9K supernatants from PB-pretreated rats were less able to activate DMN than those from controls. The 9K supernatants from $CoCl_2$-treated animals had a markedly decreased capacity for DMN activation, but only a moderately decreased one for microsome activation. These results suggest that there are multiple pathways for DMN metabolism and activation, only some of which are dependent on cytochrome P450. (29 refs)

78-5604 **Proliferating Cell Populations in the Early Phase of Dimethylnitrosamine-induced Renal Carcinogenesis.** (Eng) Hard, G. C. (Baker Medical Res. Inst., Commercial Road, Prahran, Victoria 3181, Australia). *In: Prevention and Detection of Cancer. Proceedings of the Third International Symposium on Detection and Prevention of Cancer Held by the International Study Group for the Detection and Prevention of Cancer in New York, April 26 - May 1, 1976.* International Study Group for the Detection and Prevention of Cancer. (New York, NY): Vol. 2(Part 1), 2404 pp.; 1267-1272; 1978.

Wistar rats were given a single 60-mg/kg ip injection of dimethylnitrosamine (DMN) and then sacrificed sequentially on successive days for 3 wk after being pulsed ip with ^{3}H-thymidine. Kidneys were prepared for autoradiography 1 hr after sacrifice. The precentages of labeled cells in each subpopulation representing cells involved in DNA synthesis at each daily interval were correlated with the prevailing tissue changes at that time. The only cells stimulated by DMN treatment to engage in substantial waves of increased proliferative activity in the acute phase of injury (cortical fibrocytes, proximal and distal tubule lining cells) were the same as those

from which the resulting tumors (mesenchymal and cortical epithelial tumors, respectively) are thought to be derived. The greater proportion of responding cells in the mesenchymal cell population may be relevant to the subsequent high incidence of mesenchymal tumors in relation to cortical epithelial tumors induced by DMN, and it may imply a larger hit on interstitial target cells than on epithelial cells by DMN. (9 refs)

78-5605 **Enhancement of Liver and Kidney Carcinogenesis by Dimethylnitrosamine in Thyroidectomized NZR/Gd Rats.** (Eng) Noronha, R. F. (Dept. Surgery, St. Louis Univ. Sch. Medicine, St. Louis, MO); Goodall, C. M. *In: Prevention and Detection of Cancer. Proceedings of the Third International Symposium on Detection and Prevention of Cancer Held by the International Study Group for the Detection and Prevention of Cancer in New York, April 26 - May 1, 1976.* International Study Group for the Detection and Prevention of Cancer. (New York, NY): Vol. 2(Part 1), 2404 pp.; 1273-1282; 1978.

The effect of thyroidectomy on dimethylnitrosamine (DMN) carcinogenesis was studied in inbred male and female NZR/Gd albino rats. The rats were surgically thyroidectomized (Th-x) at age 40 days and, together with intact rats, injected ip with 20 mg/kg DMN at age 85 days. Renal tubular neoplasms were induced in 20/45 and liver tumors in 8/45 intact rats following DMN treatment. In Th-x rats, 34/49 rats developed renal epithelial tumors, 29/49 rats liver tumors. Alveologenic lung tumors occurred in 44% of the intact rats and in 47% of the Th-x rats. There was a significant sex difference in intact rats, with 70% of males and 16% of females having lung tumors. There was no sex difference in lung tumor incidence in the Th-x group. Mortality from malignant renal and liver tumors in Th-x rats was significantly greater than that in the intact group. It is suggested that tissue-carcinogen interactions are altered at the stage of oncogenic initiation in Th-x animals due to modification of the metabolism and excretion of injected DMN. It is also suggested that local metabolism of DMN in responding tissues may be of greater significance to oncogenesis than systemically distributed metabolic products arising in the liver. (24 refs)

78-5606 **Interaction of Vitamin E and Selenium with the Hepatotoxic Agent Dimethylnitrosamine.** (Eng) Skaare, J. U. (Dept. Pharmacology and Toxicology, Veterinary Coll. Norway, Postbox 8146, Oslo Dept., Oslo 1, Norway); Nafstad, I. *Acta Pharmacol Toxicol (Kbh)* 43(2): 119-128; 1978.

The effects of vitamin E and selenium on the acute hepatotoxicity of dimethylnitrosamine (DMNA) were determined in six groups of male albino rats. Groups 1 and 4 received vitamin E (0.02% wt/wt) in the diet for 50 days + a single dose of 200 mg sc 48 hr before a single dose of DMNA (30 mg/kg ip) or vehicle (saline), respectively. Groups 3 and 6 were giv a single dose of 0.5 mg/kg sc ip 48 hr before DMNA vehicle, respectively. Group 2 received vehicles only, a Group 5 received oil vehicle 48 hr before DMNA. Rats w killed 24 hr after the last injection. In Group 1, vitamin ameliorated the acute hepatotoxicity of DMNA, as reflect in reduced plasma asparagine-aminotransferase (AspAT) tivity. This effect was confirmed histologically. DMNA s nificantly increased hepatic vitamin E levels in these rats, it had no effect on plasma levels. In Group 3, Se enhanc the acute hepatotoxicity of DMNA, as reflected in increas AspAT activity. This effect was not confirmed morpholo cally. DMNA did not have any effect on hepatic Se leve however, Se decreased hepatic and plasma tocopherol leve Vitamin E and Se may interfere with DMNA metabolism accelerating DMNA biotransformation or by producing ternative metabolic pathways, leading to less or more to end products. Finally, a special function of vitamin E m be to protect membranes from DMNA damage. (51 refs)

78-5607 **Effect of Hypophysectomy on Persistence Methylated Purines in Rat Liver Deoxyribon cleic Acid after Administration of Dimethylnitrosamin** (Eng) Pegg, A. E. (Dept. Physiology, Specialized Cancer R Center, Milton S. Hershey Medical Center, 500 Univers Drive, Hershey, PA, 17033); Hui, G.; Rogers, K. J. *Bioch Biophys Acta* 520(3): 671-678; 1978.

The effect of hypophysectomy and subsequent growth ho mone (1 mg/kg sc) treatment on the formation of methylat purines in the liver DNA of Sprague-Dawley rats treat with dimethylnitrosamine (DMNA: 1 or 10 mg/kg ip) w investigated. In control and hypophysectomize DMNA-treated rats, the major products were 7-methylgu nine (7-MG) and O^6-methylguanine followed by 3-methylad nine (3-MA), 7-MA, 1-MA, and 3-MG. Levels of 7-M 3-MG, 7-MA, 3-MA, and 1-MA were slightly greater th control levels in hypophysectomized rats (expected due enlarged livers), but levels of O^6-MG were significantly grea er than control levels. This was due to the slower rate of lo of O^6-methylguanine from the DNA of the hypophysect mized animals. The rate of loss of all other purines was rel tively fast and did not differ significantly between experime tal and control animals. Growth hormone treatment hypophysectomized rats decreased DNA O^6-methylguanin levels but had no effect on 7-MG levels, which suggested th the hormone increased the activity of the enzymatic syste that removes O^6-MG from DNA. Although this hormone w able to restore partial activity to the O^6-methylguanine exc sion system, other factors, possibly hormonal, are apparent required for full activity. (32 refs)

78-5608 **Formation of Dimethylnitrosamine in Pollute Environment and the Role of Photosynthet Bacteria.** (Eng) Kobayashi, M. (Dept. Agricultural Chemi

yoto Univ., Kyoto 606, Japan); Tchan, Y. T. *Water Res* 199-201; 1978.

ation of sludge with a fish meat medium, to simulate uted environment, revealed that dimethylnitrosamine N) was formed during putrefaction. However, this com- was metabolized upon addition of the photosynthetic ia *Rhodopseudomonas capsulata* to the medium. Rats hen given DMN in their drinking water with or without cteria. Liver tumors were prevented in rats receiving + *R. capsulata.* (11 refs)

509 **Formation of Nitrosamines from Drugs, III: Quantitative Determination of N-Nitrosodimethylamine Formed from Promethazine and Nitrite.** (Ger) Abaki, A. (Pharmazeutisches Institut der Universitat, Ammenburg 4, 53 Bonn-Endenich, W. Germany); Lauvetje, A. K.; Roth, H. J. *Arch Pharm (Weinheim)* 0): 775-779; 1978.

formation of N-nitrosodimethylamine (NDMA) by reaction of promethazine with sodium nitrite in HCl at 37 C was mined quantitatively by a polarographic technique. MA concentrations of 5 x 10^{-6} M could be determined. fering depolarizing agents were eliminated by vacuum lation below 60 C. (no refs)

610 **Possible Nitrosodimethylamine Formation in Comparative In Vitro Nitrosation Experiments Six Different Tetracycline Antibiotics.** (Eng) Roper, H. itut fur Organische Chemie und Biochemie der Univer- Hamburg, 2000 Hamburg 13, W. Germany); Heyns, K. *C Sci Publ* (19): 219-237; 1978.

hydrochlorides of tetracycline (TC) and six of its derivas were reacted with sodium nitrite for 2 hr at 37 C in eous buffer solns at pH 2 and 4 under simulated stomach ditions. Minocycline (MC), doxycycline (CD), oxytetraine, and anhydrochlorotetracycline (AHCTC) formed itrosodimethylamine (NDMA) in 0.02%-2.0% yields, as cted by gas-liquid chromatography. NDMA formation n MC and DC was blocked 97% by ascorbic acid. In osation experiments with MC and a thiocyanate catalyst, yields (0.5%-0.6%) were close to those of the noncatzed reaction (0.5%-0.7%). However, the possibility of an eleration of the reaction during the initial phase cannot liscounted, as NDMA levels were measured after a reac- time of 2 hr. The different reactivities of the tested TC's ard nitrite in acidic solns can be explained stereochemiy. The failure of dealkylative nitrosation reactions to oc- with TC, chlorotetracycline, and desmethylchlorotetraline is due to the formation of intramolecular hydrogen dge linkages between epidimethylamino groups at C-4 and groups at C-6. An electrophilic attack of NO+ on the ethylamino nitrogen is hindered, and NDMA formation is not possible. This hypothesis was proved by the formation of NDMA from AHCTC and sodium nitrite at pH 2. (59 refs)

78-5611 **Mechanism of N-Nitrosodimethylamine Formation from Trimethylamine and Trimethylaminoxide.** (Eng) Ohshima, H. (Dept. Biomedical Res. Food, Natl. Inst. Health, Tokyo, Japan); Kawabata, T. *IARC Sci Publ* (19): 143-153; 1978.

The kinetics of the in vitro nitrosation of trimethylamine (TMA) and trimethylaminooxide (TMAO) to produce N-nitrosodimethylamine (NDMA) was studied. TMA or TMAO (both, 0.5 millimole) was reacted with sodium nitrite (2.5 millimoles) in a pH range of 1-7 and at temperatures of 25-100 C for 2 hr. The formation of NDMA was max at pH 3 and 100 C, with yields as high as 53% being produced from TMA, 55% from TMAO. At < 75 C, the pH dependence of the nitrosation was similar to that observed with alkylamides. The initial rate of NDMA formation from TMAO at pH 3 and 25 C was proportional to the TMAO and nitrite concentrations, but not to the square of the nitrite concentration. In contrast, the rates of NDMA formation from TMA and TMAO at pH 3 and 100 C were proportional to the square and the cube, respectively, of nitrite concentration. The mechanisms of the nitrosation of TMA and TMAO were very complex, and the pathways of NDMA formation differed according to pH and temperature. At higher temperatures NDMA formation may involve oxidative cleavage of tertiary amines to produce secondary amines (dimethylamine, DMA), which may react with nitrite to form NDMA. At lower temperatures, however, NDMA may be formed from TMA or TMAO by a pathway not involving DMA. (14 refs)

78-5612 **Acceleration of Nitrosamine Formation at pH 3.5 by Microorganisms.** (Eng) Archer, M. C. (Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, MA); Yang, H. S.; Okun, J. D. *IARC Sci Publ* (19): 239-246; 1978.

The effects of microorganisms on nitrosamine formation at acidic pH, conditions of relevance to nitrosation of amines in the stomach, were investigated. When 20 mM dihexylamine (DHA) was nitrosated at pH 3.5 in the presence of 12 mg/ml *Saccharomycopsis lipolytica, Saccharomyces cerevisiae, Escherichia coli,* or *Bacillus brevis* cells, the rate of dihexylnitrosamine formation was enhanced 12-49 times over that without the bacteria or yeast cells. Rates were similar in the presence of either boiled or unheated cells. As the alkyl chain length of the secondary amine increased, the magnitude of the rate enhancement also increased, with DHA having the greatest rate acceleration. Nitrosation of the heterocyclic secondary amines morpholine and piperidine was not affected by the cells. Sonic disruption of *E. coli* cells followed by centrifugation showed that the particulate fraction was responsi-

ble for 80% of the acceleration effect, the soluble cell fraction for 20%. A nonenzymatic mechanism involving hydrophobic interactions of the precursor amines and cellular constituents is proposed. (15 refs)

78-5613 **N-Nitroso Compounds from the Reaction of Primary Amines with Nitrite and Thiocyanate.** (Eng) Tannenbaum, S. R. (Dept. Nutrition and Food Science, MA Inst. Technology, Cambridge, MA); Wishnok, J. S.; Hovis, J. S.; Bishop, W. W. *IARC Sci Publ* (19): 155-159; 1978.

When primary amines are reacted with nitrite ion in the presence of thiocyanate ion, large numbers of thermal energy analyzer-positive compounds are formed, some of which are likely to be N-nitroso derivatives. Since nitrate and thiocyanate are found in human saliva and primary amines are widely distributed in food, these reactions are of significance in the context of human cancer. (9 refs)

78-5614 **Formation In Vivo of Traces of Volatile N-Nitrosamines in the Cow after Direct Administration of Nitrate into the Rumen--Preliminary Communication.** (Eng) van Broekhoven, L. W. (Center Agrobiological Res., Wageningen, Netherlands); Stephany, R. W. *IARC Sci Publ* (19): 461-463; 1978.

N-Nitrosamine formation was investigated in the digestive tract of a quadruple-fistulated cow with a fistula in the rumen. The cow was fed a low-nitrate hay diet and then 260 mg/kg potassium nitrate, directly into the rumen. The variable amounts of N-nitrosodiethylamine, N-nitrosopyrrolidine, and N-nitrosodimethylamine detected in rumen fluid correlated with nitrite formation as a function of time after nitrate administration. (31 refs)

78-5615 **The Intake of Nitrate, Nitrite, and Volatile N-Nitrosamines and the Occurrence of Volatile N-Nitrosamines in Human Urine and Veal Calves.** (Eng) Stephany, R. W. (Natl. Inst. Public Health, Bilthoven, Netherlands); Schuller, P. L. *IARC Sci Publ* (19): 443-460; 1978.

The occurrence of volatile N-nitrosamines (NA's) in 100 total diets, 19 cheese samples, 30 veal calves fed nitrate-rich (16,400 mg/kg KNO_3) diets, and in the urine of 14 kidney stone patients medicated with massive doses of ammonium nitrate (equivalent to up to 180 mg/kg KNO_3) was evaluated by gas chromatography-thermal energy analysis. N-Diethylnitrosamine (NDMA) was frequently found in all samples, at concentrations < 1 μg/kg except for two diets (1.2 and 1.7 μg/kg). Other NA's were found sporadically in the same concentration range except for one diet having an N-nitrosopyrrolidine concentration of 1.9 μg/kg. The mean daily intake of NDMA, KNO_3, and $NaNO_2$ from the total was calculated to be 0.5 μg, 215 mg, and 7.7 mg, respecti NA recoveries were mostly at the 1-μg/kg level. There no correlation between NDMA levels and the compos of the diets or the nitrate load of the patients or veal ca Although the patients received KNO_3 doses that were 2 times the mean daily intake of dietary nitrate, NA leve the urine were not extraordinary. In addition, there wer significant differences in NDMA levels between tissu nondosed and dosed calves. The KNO_3 and $NaNO_2$ leve 142 vegetable samples and 48 human saliva samples colle at various times after the intake of vegetable-rich meals determined. Some vegetables had high to very high ni levels, but the vegetables contained only traces of nitrite. vary nitrite content was highly dependent on dietary in of nitrate and it increased up to 60 times after the consu tion of vegetable-rich meals. (29 refs)

78-5616 **New Data from Collaborative Studies on A ysis of Nitrosamines.** (Eng) Castegnaro, M. ternational Agency Res. Cancer, Lyon, France); Walke A. *IARC Sci Publ* (19): 53-62; 1978.

The results of collaborative studies of the analysis of vol and nonvolatile nitrosamines (NA's) are reported. In the study, 18 laboratories analyzed heavily spiced processed spiked with N-nitrosodimethylamine (DMNA), N trosodiethylamine, N-nitrosodibutylamine, and N trosopyrrolidine. Preliminary mass spectrometric (MS) showed that the unspiked meat contained measureable l of DMNA and N-nitrosopiperidine. The analytical t niques used included MS, gas chromatography (GC), the energy analysis (TEA), and other chemiluminescence t niques. The chemiluminescence methods (including T were as accurate as GC or MS for trace quantities of N The results indicated that volatile NA's may be determ in spiced, processed meat samples without special diffic by several established methods. In the second st freeze-dried solns of three nonvolatile NA's (N-nitrososa sine, N-nitrosoproline, and N-nitrosohydroxyproline) analyzed by 12 laboratories. Participants were provided a tube containing a known amount of each NA and one taining comparable but unknown amounts. The analy methods used included high-pressure liquid chrom graphy or GC plus detection by UV or TEA, differe pulse polarography, and thin-layer chromatogra followed by fluorimetric detection. The results indic that a sufficient number of laboratories are able to form this analysis and are able to be involved in a c borative study of nonvolatile NA's in food matrix refs)

78-5617 **Rapid Formation of N-Nitrosamines from trogen Oxides under Neutral and Alkaline C ditions.** (Eng) Challis, B. C. (Chemistry Dept., Impe Coll., London, England); Edwards, A.; Hunma, R. R.; K

ilos, S. A.; Outram, J. R. *IARC Sci Publ* (19): 127-142;

ormation of N-nitrosamines (NA's) under a wide range nditions is demonstrated. At pH 6-14 and at 25 C, NA's very rapidly in organic solvents from N_2O_3 to N_2O_4. e reactions are much faster than those with acidified ni- 2×10^{-3} M amine gives approx 10%-50% NA in a few nds with an excess of nitrogen oxide. NA yields are not red with diluted nitrogen oxides (1,000 ppm) and moder- basic amines (ie, N-methylpiperazine) react readily at iological pH. Reaction mechanisms are discussed with cular reference to the existence of two reactive tautomet- rms of N_2O_3 and N_2O_4. The formation of NA's from NO hanol at 25 C is also reported. These reactions are slow e absence of air (O_2), I_2, or metal salts. O_2 accelerates sation by converting NO (via NO_2) to N_2O_3 or N_2O_4, but I_2 and metal salts are effective under anaerobic condi-, in which reaction rates are independent of amine basici- ut dependent on the nature of the reagent. The most tive substance is I_2, which gives quantitative yields of NA few minutes at 25 C by forming the reactive nitrosyl de (NOI) reagent. Acceleration in ethanol is also ob- ed with several metal salts, with substantial amounts of being produced in 30-300 min. Metal iodides intervene he NOI reagent, as for I_2, but other salts require a mech- m involving reaction between a metal-amine complex and itself. The relevance of NA formation to human exposure scussed, with particular reference to urban pollution and effect of dietary antioxidants. (34 refs)

5618 **Possible Breakdown of Volatile N-Nitrosamines by Enzymatic and/or Microbiological Agents in ss Raw Sausage.** (Eng) Hauser, E. (Swiss Federal Veteri- y Office, Berne, Switzerland); Heiz, H. J. *IARC Sci Publ*): 289-296; 1978.

possible degradation of four added nitrosamines nitrosodimethylamine (DMNA), N-nitrosodiethylamine ENA), N-nitrosopiperidine (NPIP), and N-nitrosopyrroli- e (NPYR)] in sodium nitrate-containing Italian salami s investigated. Two of the four salamis contained starting ture (micrococcus and lactobacillus) and two contained ppb of each nitrosamine. Each of the four salamis was mpled at 0, 3, 7, 14, 21, and 29 days. Nitrosamine content s determined by gas chromatography (GC) coupled with hermal energy analyzer and by GC-mass spectrometry. MNA and DENA decreased over the 29-day ripening peri- and the decrease was enhanced over the first 21 days by addition of starting culture. On day 29, however, salamis e of starting culture and those with starting culture had same total degradation. NPIP and NPYR levels fell rap- y until day 7 and then they rose to their original amounts day 21 (NPIP) and day 14 (NPYR). Thereafter, they both opped to about half the initial amount. The use of starting ltures had no influence on total degradation. Thus, all the trosamines were partly degraded during the ripening peri- od, with the aliphatic compounds being less stable than the heterocyclic ones. (no refs)

78-5619 **Determination of Nitrosaminoalcohols and Amines by Fluorine-19 Nuclear Magnetic Resonance of Hexafluoroacetone Derivatives.** (Eng) Gaffield, W. (Western Regional Res. Center, Agricultural Res. Service, US Dept. Agriculture, Berkeley, CA); Lundin, R. E. *IARC Sci Publ* (19): 87-95; 1978.

Fluorine-19 nuclear magnetic resonance (NMR) data for several hexafluoroacetone adducts of nitrosamino alcohols and amines were obtained by Fourier transform (FT) ^{19}F NMR spectroscopy. The spectra readily differentiated among stereoisomers and positional isomers. The FT method has great potential for signal/noise enhancement, and FT NMR is approx 20 times more sensitive than continuous wave NMR for studies of a spectral range similar to that reported. (9 refs)

78-5620 **Detection and Determination of Volatile and Non-Volatile N-Nitrosamines by Thin-Layer Chromatography Using Fluorescamine.** (Eng) Young, J. C. (Chemistry and Biology Res. Inst., Agriculture Canada, Ottawa, Ontario, Canada). *IARC Sci Publ* (19): 63-73; 1978.

Volatile and nonvolatile N-nitrosamines (NA's) were analyzed quantitatively by chromatography on thin-layer plates of activated silica gel in one of three solvent systems. The NA's were cleaved to primary or, in a few cases, secondary amines and to keto compounds by UV radiation, and the amines were subsequently detected as fluorescent spots after treatment with the primary amine-specific reagent fluorescamine. Detection limits of 10-15 nanograms (approx 75 picomoles) were observed for most NA's. The method was sensitive to volatile NA's, nonvolatile N-nitrosamino acids, and the N-nitroso derivative of the herbicide glyphosate. Unfortunately, detection limits were poorest for the volatile NA's of greatest interest (dimethyl-, diethyl-, and pyrrolidinyl-). The high limits were probably due to evaporative loss of the volatile parent NA and/or the resulting primary amine. Plots of relative fluorescence vs nanomoles of NA were close to linear, so that NA concentrations could be quantitated. Applications of the method are given. (24 refs)

78-5621 **An Examination of Some Foodstuffs for Trace Amounts of Volatile Nitrosamines Using the Thermal Energy Analyzer.** (Eng) Gough, T. A. (Lab. Government Chemist, London, England). *IARC Sci Publ* (19): 297-304; 1978.

A wide range of foodstuffs was examined for trace amounts of nitrosamines (NA's) by chemiluminescence using a ther-

mal energy analyzer (TEA). Many of the 264 samples had been examined previously by mass spectrometry and shown to contain no NA's at levels > 1 μg/kg. All eight fried bacon samples contained 1-10 μg/kg N-nitrosodimethylamine (DMNA) and N-nitrosopyrrolidine (NPYR), 0.08-0.25 μg/kg N-nitrosoethymethylamine (PNIP) and 0.3-0.5 μg/kg of an unidentified NA. N-Nitrosoethylmethylamine and N-nitrosodiethylamine also occurred often in cured meats up to 0.2 μg/kg. The only NA detected frequently in the other food samples was DMNA, which was sometimes present up to 0.2 μg/kg. Other volatile NA's were rarely found, and their contribution to the total volatile NA content of food is negligible. The unidentified NA's sometimes detected by TEA do not contribute significantly to intakes, except, possibly, those in cured meats. Cured meat, fish, and cheese contained an av dialkyl-NA level about 1 order of magnitude higher than that in all the other foods examined. The only significant contribution of NPYR and NPIP to the diet is from cured meats, as, in all other samples, these NA's were detected in only a few instances in amounts > 0.01 μg/kg. (13 refs)

78-5622 **Observations on the Use of the Thermal Energy Analyzer as a Specific Detector for Nitrosamines.** (Eng) Fiddler, W. (Eastern Regional Res. Center, Agricultural Res. Service, US Dept. Agriculture, Philadelphia, PA); Doerr, R. C.; Piotrowski, E. G. *IARC Sci Publ* (19): 33-39; 1978.

Since most nitrosamines (NA's) undergo photolytic decomposition when exposed to UV light, this property was used to develop an analytical method for NA's sensitive to picogram levels. After photolysis, NA determinations are performed on a gas-liquid chromatography interfaced with a thermal energy analyzer. This technique is intended not to replace but to supplement mass spectrometric confirmation. (14 refs)

78-5623 **Survey of Cured Meat Products for Volatile N-Nitrosamines: Comparison of Two Analytical Methods.** (Eng) Havery, D. C. (Dept. Health, Education and Welfare, Washington, DC); Fazio, T.; Howard, J. W. *IARC Sci Publ* (19): 41-52; 1978.

A total of 106 cured meat samples were analyzed by multidetection gas liquid chromatography-mass spectrometry and the mineral oil distillation-thermal energy analyzer method for volatile N-nitrosamines. From 5 to 75 ppb N-nitrosopyrrolidine were found in fried bacon, and traces of N-nitrosodimethylamine were found in various cooked meats. The two techniques produced comparable results, especially at the 10-ppb level. (24 refs)

78-5624 **Determination of N-Nitrosamine Levels in Meat and Some Meat Products.** (Rus) Pokrovskii, A. A. (Inst. Nutrition, Moscow, USSR); Kostiuk Ia. L.; Melamed, D. B.; Medvedev, F. A. *Vopr Pita* 65-72; 1978.

Gas chromatography/mass spectrometry was used to trace amounts of N-nitrosamines (NA) in food product sensitivity of the method was 3 nanograms. The amo NA in various meat products ranged from 0.9 to 23.4 (the highest amount was found in pork sausage). NA not found in meat. (16 refs)

78-5625 **Electronic Properties of the Nitrosamine tion.** (Eng) Lyle, R. E. (Dept. Chemistry, Texas State Univ., Denton, TX); Fribush, H. M.; Ly G.; Saavedra, J. E. *IARC Sci Publ* (19): 99-107; 1978

The interaction of nitrosamines (NA's) with an oxidati zyme was detected by studying the effect of chiral subst capable of hydrogen bonding on the circular dichroism in the presence of achiral NA's. The addition of a alcohol to an achiral NA causes a dissymmetric perturb of the symmetrical chromophore, and a Cotton effect dent in the CD curve at the wavelength of UV absorpti the NA function. Structural implications are considere refs)

78-5626 **Chemical Models for Possible Nitrosamin tifact Formation in Environmental Ana** (Eng) Angeles, R. M. (Carcinogen Metabolism and Toxi gy Branch, NCI, Analytical Chemistry Section, Beth MD, 20014); Keefer, L. K.; Roller, P. P.; Uhm, S. J. *Sci Publ* (19): 109-115; 1978.

Two recent discoveries concerning artifact formation i analysis of nitrosamines were made: (1) solid-phase inor nitrite can efficiently nitrosate amines in the presence o tain common solvents, and (2) deionized water can co significant quantities of nitrosamines. Possible implica of both phenomena are discussed, along with measure their control. (12 refs)

78-5627 **Comprehensive Analytical Procedures fo Determination of Volatile and Non-volatile lar and Non-polar N-Nitroso Compounds.** (Eng) Fan, (Thermo Electron Res. Center, Waltham, MA); Krull, Ross, R. D.; Wolf, M. H.; Fine, D. H. *IARC Sci Publ* 3-17; 1978.

Comprehensive methods for the quantitative analysis of tile and nonvolatile, polar and nonpolar N-nitroso pounds combine the use of thermal energy analysis high-pressure liquid chromatography or standard chromatogrphy. However, independent techniques ar quired to confirm the results. (25 refs)

528 **Characteristics of the TEA Detector in Use with High Pressure Liquid Chromatography.** (Eng) , J. K. (Dept. Medicinal Chemistry, Sch. Pharmacy, Mississippi, University, MS); Ma, C. Y. *IARC Sci Publ* 19-32; 1978.

se of a thermal energy analyzer detector in conjunction high-pressure liquid chromatography for determining roso compounds is described in detail, particularly the ting parameters of the detector. The detector response ighly dependent on furnace temperature, the flow rate gas used to purge the furnace, and the volatility of the ounds. (4 refs)

529 **Non-volatile N-Nitroso Compounds in Human Feces.** (Eng) Varghese, A. J. (Ontario Cancer Toronto, Ontario, Canada); Land, P. C.; Furrer, R.; , W. R. *IARC Sci Publ* (19): 257-264; 1978.

nature of the previously detected mutagens in human was investigated. Samples were collected from healthy, noking men and they were frozen and extracted with The extracts were dried, reconstituted in ether, passed gh a 0.5-μm millipore filter, and purified by silica gel natography followed by high-pressure liquid chromaphy. The mutagenicity of the purified mutagen was con- d in the Ames assay using *Salmonella typhimurium* TA100 without microsomal activation. The exact ical nature of the mutagen could not be determined. ever, the following evidence suggests that it could be an roso compound: the mutagenically active ether extracts ted nitrite upon heating, these extracts contained al- ng agents and at least four new ninhydrin-positive com- ds, and signals for nitroso compounds were seen in the al ether extract and in the mutagen fraction by thermal y analysis. Additional evidence was provided by a diet iment based on the fact that ascorbic acid inhibits nitro- in vitro and in vivo. A volunteer was given 1 g ascorbic before each meal and at bedtimes for 2 wk. In feces cted 1 wk prior to the experiment, the level of nitroso ounds averaged 0.45 A/g feces and mutagenic activity 480 revertants/plate. After 2 wk of ascorbic acid, the so levels decreased to 0.2 A/g and the revertants ped to 160/plate. Nitroso compounds in the bowel are ably formed in the stomach or small bowel, and they may e agents responsible for cancer of the colon. (21 refs)

530 **Some Effects of Phenol- and Thiol-Nitrosation Reactions of N-Nitrosamine Formation.** (Eng) es, R. (Ministry Agriculture Fisheries and Food, Food -Colney, Colney Lane, Norwich NR4 7UA, England); is, M. J.; Massey, R. C.; McWeeny, D. J. *IARC Sci Publ* 183-197; 1978.

lts of recent studies showing that phenols and thiols can lead to enhanced nitrosamine (NA) formation under conditions in which it would not normally take place are reported. C-Nitrosophenols, produced by the nitrosation of phenols, catalyze NA formation. The rate of nitrosation of pyrrolidine catalyzed by p-nitroso-o-cresol was fastest at about pH 5. The catalytic species is thought to be the quinone monoxime tautomer of the nitrosophenol. The catalysis may involve initial nitrosation of the catalyst, either in or via the quinone monoxime tautomeric form, to give an intermediate that then undergoes attack by the amine to give NA and to regenerate the catalyst. When pyrrolidine was reacted with nitrite at pH 5.0, N-nitrosopyrrolidine was further enhanced when the reaction was performed under anaerobic conditions. Nitrosocysteine (NC) HCl reacted with N-methylaniline at pH 2.65, 5.5, and 9.75 in the absence of nitrite to give N-nitroso-N-methylaniline. The yield of the latter was reduced significantly at pH 9.75 under anaerobic conditions. NC HCl also nitrosated morpholine and pyrrolidine at pH 9.75. The rate of the reaction at this pH decreased with increasing amine basicity. The implications of these results in terms of the formation of NA's in cured meats and in vivo are not clear. The complicating effects of other components and of adsorption in heterogeneous systems cannot be predicted quantitatively. (15 refs)

78-5631 **Fate of Nitrate and Nitrite in Saliva and Blood of Monkey Administered Orally Sodium Nitrate Solution, and Microflora of Oral Cavity of the Monkey.** (Jpn) Hayashi, N. (Natl. Inst. Hygienic Sciences, 18-1, Kamiyoga 1-chome, Setagaya-ku, Tokyo, Japan); Watanabe, K.; Ishiwata, H.; Mizushiro, H.; Tanimura, A.; Kurata, H. *J Food Hyg Soc Jpn* 19(4): 392-400; 1978.

The fate of nitrate (NO_3) and nitrite (NO_2) in monkey saliva was investigated in five monkeys (2.5-5.0 kg) that were fed by stomach tube with 4, 20, and 40 mg/kg of sodium nitrate ($NaNO_3$) at 10-day intervals. The monkeys were then designated as very good (M1), good (M2 and M3), or poor converters (M4 and M5). To obtain more detailed information about the reduction of ingested NO_3, further investigation was performed on the M1 monkey, with M4 and M5 monkeys serving as controls. All monkeys were fed a 100 mg/kg $NaNO_3$ soln by stomach tube. NO_3 and NO_2 concentrations in blood and saliva were calculated. Parallel with this experiment, a comparative survey of oral microflora in the monkeys was conducted. Blood NO_3 concentrations in all monkeys peaked 7 hr after ingestion (180 ppm). In the M1 monkey, about 70 ppm was maintained for 48 hr after administration. Salivary concentrations in the M1 monkey showed a max of 800 ppm after 7 hr, and the salivary NO_3 concentration was consistently higher than that in blood. The M4 and M5 monkeys, in contrast, exhibited a lower concentration of NO_3 in blood. Salivary NO_2 in the M1 monkey reached a max concentration of 30 ppm, and 10-20 ppm was maintained in saliva for 24 hr. In the M4 and M5 monkeys, no apparent correlation between ingestion of NO_3 and formation of NO_3 in saliva was observed. Counts of bacteria and molds in the oral

cavity of the M1 monkey showed a consistently greater number of microbes than in the M4 and M5 monkeys. *Streptococcaceae, Peptococcaceae,* and *Bacteroidaceae* predominated in the oral cavity of the M1 monkey, and *Bacteroides melaninogenicus* was the most common species among the microflora. NO_3^- reducing anaerobic bacteria, ie, *Bacteroidaceae* and *Veillonella,* seemed to be indigenous in the mouth of the M1 monkey. (26 refs)

78-5632 **Gastric Juice Nitrite: Its Source and Relationship to Hydrogen Ion Concentration.** (Eng) Walters, C. L. (British Food Manufacturing Industries Res. Assoc., Leatherhead, Surrey, England); Hill, M. J.; Ruddell, W. S. *IARC Sci Publ* (19): 279-288; 1978.

Nitrite concentrations were determined in the fasting gastric juice (GJ) of 17 patients undergoing routine pentagastrin tests. Nitrite was present in the GJ from all 17 subjects, the mean concentration being 4.9 μM. Pentagastrin stimulation increased the volume and H^+ concentration of the GJ and decreased the gastrin thiocyanate concentration from a mean of 0.9 to 0.3 μM after 30-45 min. However, there was no significant change from the basal level of the mean nitrite concentration of 4.9 μM throughout the stimulation period, in spite of increased gastric aspirate volumes. In GJ and saliva, the thiocyanate levels of smokers were significantly greater than those of nonsmokers, but, there were no significant differences in nitrite levels between the two groups. Patients with demonstrable gastroduodenal lesions could be divided into normals and hypochlorhydric (HCH) normals on the basis of their fasting H^+ concentrations (> 15 and < 5 mM, respectively). Neither mean H^+ nor nitrite concentrations in the normals were significantly different from those of duodenal ulcer patients. H^+ concentrations in the GJ of HCH normals were significantly lower and their nitrite concentrations were significantly higher than those of all groups other than the six gastric cancer patients. The mean GJ nitrite concentration of the gastric ulcer patients was significantly higher than that of normal and duodenal ulcer patients, and the H^+ concentration was significantly lower. The six gastric cancer patients had a mean nitrite concentration significantly higher and an H^+ concentration significantly lower than those of the gastric ulcer group. The difference in total bacterial counts and those of nitrate-reducing organisms among the diagnostic groups were secondary to those in H^+ concentrations. (28 refs)

78-5633 **Gastric-Juice Nitrite and Gastric Cancer (Letter to Editor).** (Eng) Jones, S. M. (Univ. Dept. Surgery, Bristol Royal Infirmary, Bristol BS2 8HW, England); Davies, P. W.; Savage, A. *Lancet* 1(8078): 1355; 1978.

Among 27 patients who had undergone partial gastrectomy for duodenal ulcers, 8/10 with significant dysplasia and 2/8 with intestinal metaplasia had gastric juice nitrite concentrations $>$ 10 micromoles/liter. This finding supports t sociation between increased nitrite in the hypochlor stomach and the development of gastric carcinoma aft tial gastrectomy. (5 refs)

78-5634 **Possibility of Nitrosation During I Digestion. I. Evaluation of Precursors a fecting Factors In Vivo. II. Effect of Food Intake Reaction.** (Eng) Klein, D. (Departement de Nutrition Maladies Metaboliques, Universite de Nancy I, Nancy, ce); Gaconnet, N.; Poullain, B.; Debry, G. *IARC Sc* (19): 485-494; 1978.

The influence of ingested nitrate on concentrations of nitrate and nitrite was investigated in two groups of su only one of which swallowed their saliva. Each subje fed a 450-ml test meal containing, per 100 ml, 10 powder, 10 g glucose, 5 g corn oil, 2.2 g polyethylene and 25 mg sodium nitrate. Saliva and gastric juice sa (10 ml) were taken at 30-min intervals. Salivary nitr creased to a max (35 $\pm$ 29 mg/liter) after 90 min an declined. Salivary nitrite followed a similar course, much smaller quantity. As the meal was digested, gastr decreased from pH 5 at 30 min to pH 3 at 2 hr, and di of the alimentary bolus increased. Gastric nitrate dec in all individuals as a result of dilution. However, the nitrite concentration in subjects who swallowed their rose rapidly and reached an av value of 7 mg/liter wit min; nonswallowers displayed continued low nitrite lev is suggested that salivary nitrate is converted to nitrite esophagus. An in vitro study showed that nitrosation is ited at time of meal ingestion, but the effect is diminis the meal is diluted and digested. The results show that nitrite concentration depends essentially on the salivar tribution, which is related to the nitrate concentraton alimentary bolus. It increases during digestion and re values $>$ 10 ppm in a medium that changes in a dir favorable to nitrosation; ie, the pH decreases and the effect of the alimentary pool components diminishes. (12

78-5635 **Effects of Some Commonly Used Food tives on *Vicia Faba* Root Meristems (Me Abstract).** (Eng) Gopalan, H. N. (Dept. Botany, Ken Univ., P.O. Box 43844, Nairobi, Kenya); Njagi, G. D. *Res* 53(2): 194; 1978. (no refs)

78-5636 **Studies Related to Nitrosamide Formation rosation in Solvent: Water and Solvent Syst Nitrosomethylurea Formation in the Rat Stomach and ysis of a Fish Product for Ureas.** (Eng) Mirvish, S. S. (Ep Inst. Res. Cancer, Univ. Nebraska Medical Center, Om NE); Karlowski, K.; Sams, J. P.; Arnold, S. D. *IARC Sci* (19): 161-174; 1978.

experiments related to nitrosamide formation were cted: (1) production of nitrosamides by nitrous acid in t water mixtures and in methylene chloride (MeCl); (2) omethylurea (NMU) formation in the stomach of rats ethylurea (MU: 100 mg/kg) + sodium nitrite (4 g/kg); 3) analysis of a salt-dried bonito fish from Japan for before and after nitrosation-denitrosation by ion-exe and paper chromatography. In experiment 1, nitrous vas partly extracted from water by organic solvents, ally polar ones. Carbaryl was nitrosated 20 times faster Cl:water than in water alone, mainly because of its inlity in water. For ethylurea, hexylurea, ethyl N-ethylmate, and aminopyrine, nitrosation in sodium sulried MeCl extracts of nitrous acid at 6 C was at least complete after 5 sec. Nitrosation of N-butylacetamide) by the same extract was slower, as was nitrosation of in MeCl by equivalent concentrations of dried nitrous dinitrogen trioxide, and dinitrogen tetroxide. In experi-2, the NMU yield in rats killed 3 hr after feeding was % of the MU. When the food also contained 11.5 g/kg m ascorbate, NMU formation was inhibited completely. 2-4 g/liter $NaNO_2$ in the drinking water and MU in od, no MNU was detected. In experiment 3, the fish e contained 80 mg/kg urea but no MU. When the fish itrosated at pH 1 and then denitrosated at pH 0, 25 g MU was detected. The identity of MU was confirmed ass spectrometry. (13 refs)

537 **Methylnitrosophenylurea - A Highly Carcinogenic Compound.** (Eng) Warzok, R. (Res. p Preventive Oncology, Inst. General Pathology and ological Anatomy, Medical Acad. Erfurt, 50 Erfurt, E. many); Thust, R.; Mendel, J.; Schwarz, H.; Blaufuss, E. *Cancer Lett* 4(5): 299-303; 1978.

possible carcinogenic effects of 1-methyl -1- nitrophenylurea (MNPU), which is easily formed in from 1-methyl -3-phenylurea (MPU) and sodium e in an acid environment, were examined in ed rats of inbred strain E. The rats were given MPU, PU, or MPU plus $NaNO_2$ by a stomach tube. In the p given MPU alone, no tumors were observed in rats more than 500 days after the start of the experiment. e group given MPU plus nitrite, only four animals that before the 137th day had no tumors; the remaining 21 developed benign or malignant growths of the foreach. In the group given MNPU, 22/25 rats developed rs of the forestomach. The induction of forestomach tuin the rats given MPU and nitrite indicates that MNPU formed endogenously after administration of these two ounds. In the metabolism of the herbicide 1,1-dimethphenylurea (fenuron), MPU results as a demethylation uct. In estimating carcinogenic risk, therefore, it is not gh to investigate only the residues of methyl-substituted cides; the secondary amides formed by their demethylaeem to be of greater importance as possible carcinogenic factors (by virtue of their possible nitrosation) and should be decreased to a minimum. (10 refs)

78-5638 **Combined Transplacental Carcinogenic Effect of N-Nitrosomethylurea (NMU) and N-Nitrosoethylurea (NEU) in Rats.** (Rus) Alexandrov, V. A. (Lab. Experimental Tumors, N. N. Petrov Res. Inst. Oncology, Leningrad, USSR); Shraiber, D. *Vopr Onkol* 24(4): 38-43; 1978.

The transplacental teratogenic and carcinogenic effects of N-methylnitrosourea (MNU) and N-ethylnitrosourea (ENU) were studied in random-bred albino rats. Pregnant females received a single injection of MNU (5 or 20 mg/kg, ip), or ENU (20 mg/kg, iv) on day 13, 15, 17, or 21 of pregnancy. In another experiment, females were inoculated with MNU on day 15 and with ENU on day 17, or with ENU on day 17 and with MNU on day 21. Transplacental exposure to MNU alone induced tumors in 25% (at 5 mg/kg) and 51.5% (at 20 mg/kg) of the progeny. However, tumor incidence was greater after ENU administration: 91.2% and 86.4% after exposure on days 13 and 17, respectively. MNU + ENU induced tumors in 92.6%-95.4% of the progeny. The induced tumors were predominantly located in the CNS: of 135 CNS tumors, there were 62 oligodendrogliomas, 38 mixed oligoastrocytomas, 12 astrocytomas, 12 glioblastomas, 3 ependymomas, and 1 pinealoma. All 34 tumors of the peripheral nervous system had the histology of malignant neurinoma. MNU alone and in combination with ENU induced malformations of the CNS (microcephaly or hypoplasia of the cerebellum). The incidence of brain tumors against a background of microcephaly was 3 times greater after exposure to MNU and then to ENU than after exposure to ENU and then to MNU. (19 refs)

78-5639 **Alkylation of Deoxyribonucleic Acid In Vivo in Various Organs of C57BL Mice by the Carcinogens N-Methyl-N-nitrosourea, N-Ethyl-N-nitrosourea and Ethyl Methanesulphonate in Relation to Induction of Thymic Lymphoma. Some Applications of High-Pressure Liquid Chromatography.** (Eng) Frei, J. V. (Dept. Pathology, Univ. Western Ontario, London, Ontario N6A 5C1, Canada); Swenson, D. H.; Warren, W.; Lawley, P. D. *Biochem J* 174(3): 1031-1044; 1978.

The in vivo DNA alkylation (Alk) products of N-methyl-N-nitrosourea (MNU), N-ethyl-N-nitrosourea (ENU), and ethyl methanesulfonate (EMS) were measured by high-pressure liquid chromatography to determine whether there is a quantitative relationship between tumor yield and DNA Alk at specific sites. Female C57BL mice were injected ip with single doses of the carcinogens and sacrificed 0.5-122 hr later. Alk by the nitrosoureas was complete at 1 hr, but with EMS it was max at 2-4 hr. In addition to the rapid loss of 3- and 7-alkyladenines for all tissues, there was a rapid loss

of O^6-alkylguanines from DNA of liver that was more rapid at lower doses. In brain, lung, and kidney, excision of O^6-alkylguanine was much less marked. In thymus, bone marrow, and small bowel, all alkylated bases were lost, with half-lives of 12-24 hr at noncytotoxic Alk doses. There was no evidence for marked excision of other minor products; 1-methyladenine, O^2-ethylcytosine (found in appreciable amount only with ENU), 3-methylguanine, and dTp(Alk)dt persisted in alkylated DNA, including that of liver. In a second experiment, mice were injected ip with up to 60 mg/kg MNU, up to 240 mg/kg EN, and up to 400 mg/kg EM in order to induce thymic lymphomas. Lymphoma induction was related to the extent of Alk of the target tissues, thymus and bone marrow. Tumor yields were > 90% with 60 mg/kg MNU, < 52% with 240 mg/kg ENU, but only a few percent with 400 mg/kg EMS. The carcinogenic effectiveness of these agents was positively correlated with the extent of Alk of guanine in target tissue DNA at the O-6 atom. Assuming that at doses giving equal carcinogen response these extents of Alk would be equal, the ratio of equipotent doses to that for MNU would be 5.3 for ENU and 21 for EMS. (51 refs)

78-5640 **Tumor Induction in a Localized Area of the Hamster Trachea with N-Nitroso-N-methylurea: Effect of Exposure Conditions.** (Jpn) Yarita, T. (Div. Surgery, Inst. Pulmonary Cancer Res. Sch. Medicine, Chiba Univ., Inohana, Chiba 280, Japan); Nettesheim, P. *Haigan* 18(2): 181-194; 1978.

The tumor-response of the hamster trachea to two concentrations of N-nitroso-N-methylurea (NMU) and the number of exposures required for tumor induction were investigated. The animals were divided into four groups and given (1) 20 or (2) 30 twice-weekly exposures to 1% NMU, or (3) 20 or (4) 30 twice-weekly exposures to 0.5% NMU. A high incidence of benign tumors was observed in Group 3. The incidence of invasive carcinoma in the four groups was 67%, 94%, 39%, and 76%, respectively. Histological types resembling those seen in human lung cancer were noted. The major tumor types in Groups 1 and 2 were epidermoid and anaplastic large cell carcinomas. The lower concentration of NMU induced a higher incidence of adenocarcinoma (43% of all the invasive carcinomas in Groups 3 and 4, vs 13% in Groups 1 and 2). The mean tumor-induction period in Groups 3 and 4 was 10-14 wk longer than that in Groups 1 and 2. With 0.5% NMU, the epithelium bordering the tumors mainly underwent hyperplastic and hypertrophic changes. With 1% NMU, the main changes in the epithelium bordering the tumors were squamous metaplasia with various degrees of atypia. (30 refs)

78-5641 **Sodium Azide-mediated Recovery from N-Methyl-N-nitrosourea-induced Genetic Injury and Repair of DNA Damage in Barley.** (Eng) Gichner, T. (Inst. Experimental Botany, Flemingovo n. 2, 160 00 Prague 6, Czechoslovakia); Veleminsky, J.; Pokorny, V. *Exp Bot* 18(1): 27-31; 1978.

The sodium azide-mediated recovery of barley seed N-methyl-N-nitrosourea (MNU)-induced genetic injur ported. Dry or presoaked barley seeds were treated f 5 hr with 3-6 mM MNU, washed for 1 hr, and then for 3 hr with 40-600 mM azide at pH 7. The sodium posttreatment reduced the yield of genetic injuries seedling height reduction, M_1 sterility, and M_2 chlo mutants). The number of single-stranded break (S DNA isolated from embryos immediately after the te tion of MNU and MNU + azide treatments was appr same. However, when the isolation of DNA from M azide-treated seeds was postponed for 24 hr, a reduc MNU-induced SSB was noted. It is suggested that s azide prolonged the period between MNU-induced damage and the onset of the first semiconservative DN thesis, allowing more time for prereplication repair to (15 refs)

78-5642 **Effects of Carcinogen Dose on the Chara tics of the Tracheal Tumor Response I by N-Nitroso-N-methylurea in Hamsters.** (Eng) Yar (Dept. Surgery, Inst. Pulmonary Res., Sch. Medicine, Univ., Chiba 280, Japan); Nettesheim, P. *Int J Cancer* 298-303; 1978.

The effects of carcinogen dose on the characteristics tracheal tumors induced by N-nitroso-N-methylurea (in male Syrian golden hamsters are described. Animal exposed, via an intratracheal catheter, to 0.5% or NMU 2 x/wk for a total of 20 or 30 exposures. Dat a previous report on exposure to 1% NMU (same re are included for comparison. Most of the tumors dev in the midportion of the tracheas, and virtually all dev after the end of the 10- to 15-wk exposure period. incidence ranged from 20% to 94% with mean tumor tion times of 13-46 wk, depending on dose (ie, exposu quency x NMU concentration; total, 6 doses). Tumo dence, carcinoma incidence, and number of tumo animal were directly proportional to dose, and tumor l was inversely proportional to dose. The number of tumors (papillomas, polyps) was high at the three doses (47%-75% of all tumors) and low at the three h doses (2%-22%). The proportion of invasive carci ranged from 5% to 40% at the lower doses and 67% t at the higher doses. These included epidermoid, adeno dermoid-adeno-, and anaplastic large- and small-cel cinomas. A relatively high proportion of the ade cinomas (7/17) occurred at the three lower concentrations. The possible mechanisms of the dose of NMU are presented. (21 refs)

78-5643 **Significance of Modifying Factors in the I opment of Peripheral Nervous System T**

Rabbits. (Rus) Beniashvili, D. Sh. (Lab. Chemical Carogenesis, Inst. Oncology Georgian SSR Ministry Health, isi, USSR). *Vopr Onkol* 24(9): 60-65; 1978.

influence of modifying factors on the induction of peri-ral nervous system tumors by methylnitrosourea (MNU) studied in 170 chinchilla rabbits. MNU was introduced the ear vein in weekly doses of 10 mg/kg. Group 1 was nunized with rabbit sciatic nerve tissue homogenate (4 es of 0.3-0.7 ml at 2-wk intervals) in complete Freund's ivant; in Group 2, the sciatic nerve was chronically irritat-nechanically; Group 3 comprised females castrated before IU treatment; Group 4 comprised females treated with estrol (60 mg/kg/mo sc); Group 5 was treated with roidin (250 mg/kg/day); Group 6 was treated with mes-olyl (5 mg/kg/day po); and Group 7 served as controls. nerve tumor induction rate (number of tumors/number nimals alive at tumor appearance) was 9/21 in Group 1, 29 in Group 2, 1/15 in Group 3, 6/12 in Group 4, 1/12 Group 5, 7/14 in Group 6, and 3/16 in Group 7. The mean nt time was 485, 531, 786, 456, 751, 442, and 720 days, pectively. The tumors were identified as neurinomas (16), glioneuromas (4), neurogenic sarcomas (14), and sympa-oblastomas (5). They were localized in the sciatic nerve, vical plexus, lumbosacral plexus, and trigeminal nerve. oplasms of the brain, breast, ovaries, and thyroids were n in 14 rabbits only. The findings indicate that castration thyroidin treatment significantly reduced the tumor in-tion rate and prolonged the latent period. (14 refs)

5644 **Effect of Dietary Undegraded Carrageenan on Colon Carcinogenesis in F344 Rats Treated with oxymethane or Methylnitrosourea.** (Eng) Watanabe, K. aylor Dana Inst. Disease Prevention, American Health ndation, Valhalla, NY, 10595); Reddy, B. S.; Wong, C. Weisburger, J. H. *Cancer Res* 38(12): 4427-4430; 1978.

e modifying effect of undegraded carrageenan (CG) on on carcinogenesis induced by azoxymethane (AOM) and thylnitrosourea (MNU) was studied in weanling (5 wk) female F344 rats fed a high-fat diet containing 0% or % CG. At age 8 wk, 30 rats in each dietary group (exclud-controls) received 1 weekly sc injection of AOM (8 /kg) for 10 wk. In a separate series, 30 rats on each diet re given intrarectal injections of MNU (2 mg/rat 2 x/wk 3 wk). The AOM groups were autopsied 40 wk and the NU 30 wk after the first injection. No tumors developed ntreated rats fed the control diet; however, one untreated fed the CG diet had a single colon adenoma. The animals the CG diet and treated with AOM or MNU had a signifi-tly higher incidence of colorectal carcinoma (both number tumor-bearing rats and number of tumors per rat) than se subjected to similar carcinogen treatments but fed the ntrol diet. It is concluded that irrespective of the type of cinogen (AOM and MNU differ in mechanism of activa-n), undegraded carrageenan has an enhancing effect on orectal carcinogenesis. (20 refs)

78-5645 **Some Effects of *N*-Methylnitrosourea on the Oral and Odontogenic Tissues of the Syrian Golden Hamster.** (Eng) Edwards, M. B. (Dept. Dental Science, Royal Coll. Surgeons of England, Lincoln's Inn Fields, London WC2A 3PN, England). *Arch Oral Biol* 23(7): 515-524; 1978.

The oral and dental changes induced by the administration of N-methyl-nitrosourea (NMU, 1 mg 2x/wk for 4 wk by stomach tube) to 10 1-mo-old male and female Syrian golden hamsters were studied. The eight animals that survived 3-15 mo after treatment showed wt loss, ascites, severe epistaxis, premalignant papillomatosis of the forestomach (7/8 animals), and premalignant lesions of the oral epithelium (7/8). The latter lesions became malignant in two animals. Between 4 and 18 wk after treatment, the lower incisors became stunted, often permanently. Three hamsters developed odontogenic cysts in incisor enamel organs that had undergone squamous metaplasia. Other changes included dental dysplasia and the growth of islands of odontogenic epithelium in the periodontal ligament. Permanent dental malformation appeared to result from repetitive cytotoxic injury and the resultant hamartoplasia, complicated by a secondary metabolic deficiency of systemic origin and by permanent disturbance of induction in odontogenesis. The proliferation of epithelium in the periodontium resembled early neoplastic changes suggestive of ameloblastoma. Further consideration of the use of NMU in models of odontogenic tumor formation is warranted. (66 refs)

78-5646 **Studies on Carcinogen Chromatin-DNA Interaction: Inhibition of *N*-Methyl-*N*-nitrosourea-induced Methylation of Chromatin-DNA by Spermine and Distamycin A.** (Eng) Rajalakshmi, S. (Dept. Pathology, Univ. Toronto, Medical Sciences Building, Toronto, Ontario, Canada M5S 1A8); Rao, P. M.; Sarma, D. S. *Biochemistry* 17(21): 4515-4518; 1978.

To determine whether carcinogens interact with specific regions of DNA, the effects of spermine and distamycin on the N-methyl-N-nitrosourea (MNU)-induced in vitro methylation of rat liver chromatin were studied. Both spermine and distamycin A inhibited the MNU-induced methylation of chromatin DNA at the N^7 and O^6 positions of guanine and the N^3 position of adenine. The inhibition increased with increasing concentrations of inhibitor. Under conditions producing a 90% inhibition of chromatin DNA, the methylation of 2-deoxy-5-guanylic acid was unaffected. The results indicate that spermine and distamycin A exert their inhibitory effect by altering the structure and/or net charge of the DNA. It is suggested that MNU alkylates regions of DNA that are readily denaturable, probably A-T-rich regions located in the minor groove at or near the DNA binding sites of these two compounds. (23 refs)

78-5647 **Activities of Enzymes of the Hexose Monophosphate Pathway in Nervous System Tumors In-**

duced by Ethylnitrosourea. (Eng) Coleman, M. T. (Div. Neurology, Coll. Medicine, Ohio State Univ., 466 W. 10th Ave., Columbus, OH, 43210); Allen, N. *Acta Neuropathol (Berl)* 41(3): 223-227; 1978.

The activities of three enzymes of the hexose monophosphate pathway (HMP) were measured in samples of normal rat cerebral cortex and ethylnitrosourea-induced tumors of the rat nervous system (neurinomas, astrocytic gliomas, mixed gliomas, ependymomas, and undetermined types). In most tumors, adequate amounts of glucose-6-phosphate dehydrogenase (G6PDH), 6-phosphogluconate dehydrogenase (6PGDH), and transketolase (TK) were present so as not to be rate-limiting for utilization of the HMP. When enzyme activities were expressed on the basis of fresh wt, TK was increased in most tumors as compared with the cerebral cortex. G6PDH and 6PGDH were more variable, showing either higher or lower activities in tumors compared with controls. In general, the protein content of the tumors was lower than that of the cerebral cortices. When the activities were expressed in terms of this protein content, the mean values for the dehydrogenases in all tumor types were higher than the av value in the cortex. This indicated that G6PDH and 6PGDH were spared in tumors relative to other proteins. TK activities in tumors, expressed in terms of cytosol protein, were lower than or in the same range as those in the cortex. Increased activities of HMP enzymes in some tumors indicated that the potential activity of HMP in some (but not all) nervous system tumors is greater than that of the cerebral cortex. (21 refs)

78-5648 **Oxygens in DNA Are Main Targets for Ethylnitrosourea in Normal and Xeroderma Pigmentosum Fibroblasts and Fetal Rat Brain Cells.** (Eng) Singer, B. (Dept. Molecular Biology, Univ. California, Berkeley, CA, 94720); Bodell, W. J.; Cleaver, J. E.; Thomas, G. H.; Rajewsky, M. F.; Thon, W. *Nature* 276(5683): 85-88; 1978.

Experimental evidence that pyrimidine oxygen atoms are the major sites of reaction in cells treated with ethylnitrosourea (ENU) is presented. Three types of mammalian cells were treated with ^{14}C-ENU in cell culture in conditions of low toxicity: SV40-transformed human fibroblasts, SV40-transformed Xeroderma Pigmentosum fibroblasts, and fetal (18th day)BD IX rat brain cells. The nature and proportion of alkyl products formed in the DNA of ENU-treated cells in culture were remarkably similar to those found when DNA is alkylated with ENU to a high extent in vitro. The ethylation pattern was similar for all three cell types. The products quantified in this study were ethylphosphotriesters, 7-ethylguanine, 3-ethyladenine, O^6-ethyldeoxyguanosine, O^2-ethylthymidine, O^4-ethylthymidine, and O^2-ethylcytosine. The similarity found between the in vitro and in vivo products (with over a 1,000-fold difference in the extent of reaction) suggests the possibility of predicting in vivo reaction products of an ultimate carcinogen reacting with nucleic acids from the more easily performed in vitro studies. The formation of O-alkyl bases is likely to cause mispairing during transc tion or DNA replication and may be the initiating ever cellular mutagenesis or neoplastic transformation. (18

78-5649 **Experimental Brain Tumors Induced Trans centally by Ethylnitrosourea. V. Ultrastruct Studies Using Transmission and Scanning Electron Mic copy.** (Jpn) Taomoto, K. (Dept. Neurological Surgery, K Univ. Sch. Medicine, Ikuta-ku, Kobe 650, Japan); Fujiw K.; Tamaki, N.; Matsumoto, S. *No To Shinkei* 30(8): 911- 1978.

The ultrastructure of gliomas induced transplacentall SD-JCL rats with a single ip dose of 50 mg/kg eth trosourea (ENU) was studied by transmission and scan electron microscopy. The ENU-exposed subependymal trix layers of the fetus showed irregular and rough arra ments with expanded extracellular spaces. These cha were not seen in control rats. The subependymal layer seemed to form the "microtumor." One of the microtum found in an 8-wk-old rat, was composed of small round c The fine structure of these cells was characteristic of a pr tive oligodendroglioma. The fine structure of the subepe mal glioma cells was often pleomorphic. These gliomas tained a mixture of primitive oligodendrocytes ependymal cells plus anaplastic glial cells. With increa size, the gliomas became more pleomorphic, containi mixture of neoplastic oligodendrocytes, astrocytes, ependymal cells and ependymomalike cells with neither nor junctional complexes. The abnormal vascular struc of the tumor was confirmed by injection replica scan electron microscopy. The differences between the surfac the astrocytoma and oligodendroglioma cells were cle demonstrated. (55 refs)

78-5650 **Studies of Organ Cultures of Embryonic B Tissue (Hippocampus Region) of Rats Tre Transplacentally with N-Ethylnitrosourea.** (Rus) Golub I. (Dept. Carcinogenic Agents, Oncological Res. Cer Acad. Medical Sciences USSR, Moscow, USSR); Shabac M. *Biull Eksp Biol Med* 86(10): 496-498; 1978.

The transplacental effect of N-ethylnitrosourea (ENU: si dose of 30 or 60 mg/kg iv), administered to mongrel w rats during the last week of pregnancy, was studied in o cultures prepared from the hippocampus of embryos extr ed on the 20th day of pregnancy. The brain tissue cult proved to be highly sensitive to ENU as shown by the creased survival rate of the experimental cultures comp with the controls (82% vs 51.9%, $p < 0.001$) and the app ance of epithelial proliferations of the vascular plexus resembled adenomas. The frequency of the morpholo changes was dose-dependent: changes were found in 11/ explants from embryos treated with 30 mg/kg ENU an 37/132 explants from embryos treated with 60 mg/kg refs)

651 **The Effect of Simultaneous Treatment of *E. Coli* by Chemical Mutagens and Radiation on Mutation Rate (Meeting Abstract).** (Eng) Hotz, G. nforschungszentrum Karlsruhe, Institut fur Strahlenbi-ie, D 7500 Karlsruhe, W. Germany). *Mutat Res* 53(2): 1978. (no refs)

652 **The Effect of Expression Time on the Frequency of Carcinogen-induced Mutants at the TK HGPRT Loci in L5178Y Mouse-Lymphoma Cells eting Abstract).** (Eng) Brown, M. M. (Univ. North olina, Chapel Hill, NC, 27514); Clive, D. *Mutat Res*): 159; 1978. (2 refs)

653 **Mutagenicity of Pesticides Evaluated by Means of Gene Conversion in *S. cerevisiae* and *A. nidu-* (Meeting Abstract).** (Eng) De Bertoldi, M. (Istituto di robiologia agraria, Universita di Pisa, Pisa, Italy); Barale, Giovannetti, M. *Mutat Res* 53(2): 174-175; 1978. (no refs)

654 **Variation in the Induction of Mitotic Gene Conversion by Chemical Mutagens (Meeting Abct).** (Eng) Davies, P. J. (Dept. Genetics, Univ. Coll. nsea, Singleton Park, Swansea SA2 8PP, England); Tip- R. S.; Parry, J. M. *Mutat Res* 53(2): 173; 1978. (no refs)

655 **Detection of Chemically Induced Somatic Mutation in Tissues of Chinese Hamsters (Meeting ract).** (Eng) Dean, B. J. (Sittingbourne Res. Center, Sitbourne, Kent ME9 8AG, England); Senner, K. R. *Mutat* 53(2): 173-174; 1978. (1 ref)

656 **Effects of Mixtures of Ethyl Methanesulfonate and Caffeine or Maleic Hydrazide on Lethal uencies in *Drosophila melanogaster* (Meeting Abstract).**) Nawar, M. M. (Dept. Botany, Faculty Agriculture, ofiyah Univ., Shebeen Elkom, Egypt); Hamza, H. A. *at Res* 53(2): 240; 1978. (no refs)

657 **Mutagenicity Studies on Chemical Carcinogens (Meeting Abstract).** (Eng) Clive, D. (Genetic cology Lab., Burroughs Wellcome Co., Research Trian- Park, NC). *Mutat Res* 53(2): 169-170; 1978. (no refs)

658 **The Use of Marked Y Chromosome for Mutagenicity Testing in Drosophila (Meeting Abstract).** (Eng) Lim, J. K. (Univ. Wisconsin-Eau Claire, Eau Claire, WI, 54701). *Mutat Res* 53(2): 220-221; 1978. (no refs)

78-5659 **Quantitative Studies of Alkyl Methanesulfonate Induced Mutation in *Salmonella typhimurium* and Human Lymphoblasts (Meeting Abstract).** (Eng) Hoppe, H. (Dept. Genetics and Toxicology, Massachusetts Inst. Technology 18664, Cambridge, MA, 02139); Skopek, T. R.; Liber, H. L.; Thilly, W. G. *Mutat Res* 53(2): 200; 1978. (no refs)

78-5660 **Comparative Studies on the Relation Between Reaction Kinetics and Mutagenic Action of Monofunctional Alkylating Agents in Drosophila (In Vivo) and Chinese Hamster Cells (In Vitro) (Meeting Abstract).** (Eng) Vogel, E. (Dept. Radiation Genetics and Chemical Mutagenesis, Univ. Leiden, Leiden, Netherlands); Natarajan, A. T. *Mutat Res* 53(2): 279-280; 1978. (no refs)

78-5661 **Mutagen-sensitive Mutations of *Drosophila melanogaster* (Meeting Abstract).** (Eng) Smith, P. D. (Dept. Biology, Emory Univ., Atlanta, GA). *Mutat Res* 53(2): 265-266; 1978. (6 refs)

78-5662 **Sensitivity of Dominant Lethal Assay in Male Mice (Meeting Abstract).** (Eng) Ehling, U. H. (Abteilung fur Genetik, Gesellschaft fur Strahlen- und Umweltforschung, D-8042 Neuherberg, W. Germany). *Mutat Res* 53(2): 183; 1978. (no refs)

78-5663 **Purification and Characterisation of an *Escherichia coli* Enzyme that Releases Free 3-Methyladenine from Alkylated DNA (Meeting Abstract).** (Eng) Riazuddin, S. (Dept. Chemistry, Karolinska Inst., 104 01 Stockholm, Sweden); Lindahl, T. *Mutat Res* 53(2): 253; 1978. (no refs)

78-5664 **Somatic Mosaicism Induced by Some Carcinogens in Soybean (*Glycine max*) (Meeting Abstract).** (Eng) Arenaz, P. (Univ. Nevada, Reno, NV, 89557); Vig, B. K. *Mutat Res* 53(2): 147; 1978. (1 ref)

78-5665 **Interactions of Ionizing Radiation, Nitrosamines, Sulfonoxyalkanes and Antioxidants as**

They Affect Carcinogenesis and Survival in Mice. (Eng) Clapp, N. K. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830). *Am Ind Hyg Assoc J* 39(6): 448-453; 1978.

The effects of butylated hydroxytoluene (BHT) treatment on leukmogenesis and tumorigenesis were studied in BALB/c mice. BHT (0.75%) was added to the diet during weeks 8-12 of life; at 12 wk of age, dimethylnitrosamine (DMN), diethylnitrosamine (DEN), methyl methanesulfonate (MMS), or ethyl methanesulfonate (EMS) was given ip or the animals were x-irradiated (525 or 600 R). In another experiment, BHT was given in the feed continuously starting at 8 wk of age. In some mice, DEN (4 mg/100 ml in drinking water from weeks 11 to 18) and/or x-rays (250 R at week 11) were also administered. BHT protected the mice against acute (30-day) lethality resulting from x-irradiation or treatment with DNM, DEN, or EMS; it did not protect against the lethal effects of MMS. Survival was decreased in irradiated mice compared with nonirradiated controls, and the incidence of leukemia was increased in all irradiated groups. The incidence of leukemia was reduced in BHT-treated, irradiated animals relative to non-BHT-treated, irradiated animals. In mice treated with BHT throughout life, the compound had no effect on survival or lung tumor incidence. Survival among female mice given DEN alone was 43%; in females given DEN + BHT, it was 68%; the difference was due to a significant reduction in squamous cell carcinomas of the forestomach. BHT had no such effects in males. Radiation treatment was associated with decreased survival and an increased incidence of pulmonary adenomas; concomitant treatment with BHT nullified these effects. Treatment with DEN increased the lethality of radiation treatment, but radiation had no effect on DEN-induced pulmonary adenomas. The data suggest that the interactions among BHT and chemical and physical agents regarding late effects may occur by different mechanisms. (18 refs)

78-5666 **A Linear Relationship Between Tumorigenic Potency In Vivo and Mutagenic Potency at the Heterozygous Thymidine Kinase (TK+/-) Locus of L5178Y Mouse Lymphoma Cells Coupled with Mammalian Metabolism (Meeting Abstract).** (Eng) Clive, D. (Genetic Toxicology Lab., Burroughs Wellcome Co., Research Triangle Park, NC). *Mutat Res* 53(2): 170-171; 1978. (no refs)

78-5667 **Application of Alkaline Sucrose Gradient Sedimentation to the Study of DNA Damage and its Repair in Mammalian Cells Treated with Methylmethanesulfonate and 4-Nitroquinoline-1-oxide.** (Eng) Pavlis, R. (Dept. Biochemistry, Univ. Western Ontario London, Ontario, N6A 5C1, Canada); Yatscoff, R. W.; Sridhar, R.; Walker, I. G. *Chem Biol Interact* 23(1): 31-44; 1978.

KB human epidermoid carcinoma cells and strain L mouse cells were treated with methylmethanesulfonate (MMS, 0.1-2.0 mM) or 4-nitroquinoline-1-oxide (4 NQO, 0.05-1 μM), and the resulting DNA damage and subsequent rep were studied using sedimentation in an alkaline sucrose gra ent. The sedimentation profiles obtained resulted from a co plex interacton between drug dosage, duration of the ly period, and the repair capacity of the cells. If the numbe single-strand breaks generated during the lysis period did exceed a minimal value (on the order of 0.1 per 165S un the size of the DNA produced remained at 165S. At a grea frequency of breaks, DNA less than 165S was produced to the effect of less alkali-labile lesions. It was concluded t 4NQO and MMS produce two kinds of modifications DNA that show up as single-strand breaks during sedimen tion. One is readily alkali-labile and one is less alkali-lab Both are repaired by KB cells, but only the readily kali-labile modification can be repaired by L cells. (14 r

78-5668 **A Structure-Carcinogenicity Study of 4- troquinoline 1-Oxides Using the SIMCA Me od of Pattern Recognition.** (Eng) Dunn, W. J. (Res. Gr Chemometrics, Inst. Chemistry, Umea Univ., S-901 Umea, Sweden); Wold, S. *J Med Chem* 21(10): 1001-10 1978.

Structure-carcinogenicity data for a series of 33 4-nitro- 4-hydroxyaminoquinoline 1-oxides were analyzed by SIMCA method of pattern recognition. Eighteen of the co pounds had consistently given positive results in animal cinogenicity tests and 10 had been consistently negative. ing physicochemically based substituent constants to desc each compound, a principal components model was deri for the carcinogens. Using this model, 16/18 of the active 7/10 of the inactive compounds were correctly predicted. the seven 6-substituted compounds analyzed, a significa relationship was observed between structural parameters sociated with carcinogenic potential and ability to stimu unscheduled DNA synthesis. These results indicate that tern recognition methods can be used to assess the carci genic potential of chemical compounds on the basis of m measured variables. The differentiation between carcinog and noncarcinogens can be made on the basis of structu variables obtained from tabulated physicochemically ba substituent constants. (29 refs)

78-5669 **Mechanism of the Promotion of 4-Nitroqui line 1-Oxide-induced Lung Tumors in Mice Cigarette Smoke Condensate.** (Jpn) Yamane, Y. (Facu Pharmaceutical Sciences, Chiba Univ., Yayoi-cho, Ch 280, Japan); Sakai, K.; Katsuki, H.; Okamoto, T. *Hai* 18(2): 141-147; 1978.

The tumor-promoting effect of the neutral fraction of ci rette smoke condensate (CSC) on 4-nitroquinoline 1-ox (4-NQO)-induced mouse lung tumors was examined. Inve gation of the effect of this fraction on 4-NQO metabolism

nouse lung and liver showed that 4-NQO reductase ac- was strikingly enhanced in the mouse lung. This sug- that stimulation of 4-NQO reductase activity by the al fraction of CSC might be the mechanism whereby the tumors are promoted. (26 refs)

670 **Carcinogenicity of 4-Nitrosoquinoline 1-Oxide and Its Possible Role in Carcinogenesis by troquinoline 1-Oxide.** (Eng) Takahashi, K. (Faculty maceutical Sciences, Nagoya City Univ., Tanabedori, ho-ku, Nagoya 467, Japan); Kawazoe, Y.; Tada, M.; , M.; Ito, N.; Okada, M. *Gann* 69(4): 499-505; 1978.

carcinogenicity of 4-nitrosoquinoline 1-oxide (4-NOQO) ale ddY mice and its mutagenicity and toxicity in *Es- chia coli* were assayed. The mice received 10 weekly in- ons of 0.15 mg 4-NOQO sc. Fibrosarcomas were induced 11 mice, and they were palpable between 150 and 300 after exposure. A UV-type lesion was induced in *E. coli* treatment with 4-NOQO, and *E. coli* mutagenicity and ity increased with increasing dosage, similar to the re- obtained with 4-nitroquinoline 1-oxide (4-NQO). The ts of 4-NOQO were stronger than those of 4-NQO. DNA sarcoma-180 ascites cells grown in female ddY mice in and incubated with 2 x 10^{-4} M 4-NOQO and calf thymus A incubated with 5 x 10^{-4} M in vitro were analyzed matographically following acid hydrolysis. The DNA quinoline adducts proved to be similar with those ob- d by the action of 4-NQO in vivo. Because of the similar ities of 4-NQO and 4-NOQO, it is assumed that these nogens share a common ultimate metabolite, hypothe- to be O-aminoacyl-4-hydroxyaminoquinoline 1-oxide. efs)

671 **Misrepair Model for Carcinogenesis by 4-Nitroquinoline 1-oxide Based on Its Parallelism Mutagenesis in *Escherichia coli* (Meeting Abstract).** Kondo, S. (Dept. Fundamental Radiology, Faculty icine, Osaka Univ., Osaka 530, Japan). *Mutat Res* 53(2): 212; 1978. (no refs)

672 **Carcinogenicity of 8-Nitroquinoline in Sprague-Dawley Rats.** (Eng) Takahashi, M. (First . Pathology, Nagoya City Univ. Medical Sch., 1 asumi, Mizuho-cho, Mizuho-ku, Nagoya 467, Japan); i, T.; Fukushima, S.; Hosoda, K.; Yoshida, S.; Ito, N. *cer Lett* 4(5): 265-270; 1978.

carcinogenicity of 8-nitroquinoline given po was tested tbred Sprague-Dawley rats. The rats were fed a semisyn- diet supplemented with 250, 500, 1,000 or 2,500 ppm roquinoline for 48 wk. Twenty-eight of 180 rats died g treatment due to toxicity. In the animals that survived for 48 wk, squamous cell carcinomas of the upper digestive tract (tongue and esophagus) and, especially, of the forestomach occurred among the higher concentration groups. Squamous cell carcinomas of the forestomach occurred in 3/11 rats of the 2,500-ppm group and 7/35 rats of the 1,000-ppm group. Three cases of lung adenoma were also observed in the 2,500-ppm group. These results indicate that 8-nitroquinoline is carcinogenic in rats when administered po in a semisynthetic diet. (15 refs)

78-5673 **Inhibition of DNA Replicon Initiation by 4-Nitroquinoline 1-Oxide, Adriamycin, and Ethyleneimine.** (Eng) Painter, R. B. (Lab. Radiobiology, Univ. California, San Francisco, CA, 94143). *Cancer Res* 38(12): 4445-4449; 1978.

The effects of three different chemical carcinogens, 4-nitroquinoline (4-NQ), adriamycin (AM), and ethyleneimine (EI), on DNA synthesis in HeLa S3 cells were investigated by pulse labeling the nucleic acid with tritiated thymidine and sedimentation analysis. When administered in doses that reduced the rate of DNA replication to 30%-60% of control values, only EI produced damage that was manifest in lower mol wts of parental DNA. All three compounds inhibited replicon initiation but to differing extents. The primary causes of synthesis inhibition were as follows: 4-NQ, inhibition of replicon initiation; AM, slowing of chain elongation rate; and EI, blocked chain elongation. It is concluded that inhibition of replicon initiation is an important mechanism in the action of DNA-damaging agents in mammalian cells and furthermore, that control of DNA replication depends on the structural integrity of a chromosomal subunit that consists of several replicons. (32 refs)

78-5674 **Effect of Aluminium Chloride on Binding of 4-Hydroxyaminoquinoline 1-Oxide to Nucleic Acids.** (Eng) Yamane, Y. (Faculty Pharmaceutical Sciences, Chiba Univ., 1-33, Yayoi-cho, Chiba 280, Japan); Ohtawa, M. *Gann* 69(4): 477-486; 1978.

Aluminum chloride depressed the binding of 4-hydroxyaminoquinoline 1-oxide (4-HAQO) to DNA and RNA in the lung and liver of male dd mice and male Wistar rats. When 7 micromoles (μmol) $AlCl_3$ were preincubated with the DNA or RNA in an ice bath for 1 hr and then incubated with 0.1 ml of an HAQO reaction mixture in the presence of 3-4 μmol seryl-AMP, binding of the mouse and rat nucleic acids were depressed to approx 50% and 56%-68% of control values, respectively. Increasing concentrations of $AlCl_3$ decreased binding further. Sc injection of 1 mg $AlCl_3$ into mice, extraction of RNA and DNA from lungs and liver, and incubation with 4-HAQO resulted in a suppression of binding of lung DNA and RNA to 71.5% and 74.1% of control values. Corresponding figures for liver were 62.3% and 63.6%. Rats injected similarly with 50 mg/kg $AlCl_3$ displayed lung DNA

and RNA binding rates that were 60.2% and 44.7% of control values; liver DNA binding was 39.7% of control value. Binding rates with rat liver RNA were not significantly affected. When $AlCl_3$ (1 mg/mouse or 50 mg/kg rat) and ^{14}C-N-nitroquinoline 1-oxide (NQO) (1 mg/1 μCi/mouse or 50 mg/25 μCi/kg rat) were simultaneously injected sc on either side of the back, radioactivity measured 1 hr later was markedly depressed in lung DNA and RNA, but not in liver nucleic acids. Column chromatography demonstrated that 4-NQO severed rat lung DNA to a low-mol-wt fraction, ip or sc injection of 50 mg/kg $AlCl_3$ suppressed the DNA damage induced by ip or sc injection of 50 mg/kg 4-NQO. (23 refs)

78-5675 **Use of the Tester Strains N23 and N24 for the Detection of the Mutagenicity of Environmental Agents and Chemical Carcinogens in *Neurospora crassa* (Meeting Abstract).** (Eng) Ong, T. (Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC, 27709); Whong, W.; Guthrie, J. *Mutat Res* 53(2): 246; 1978. (no refs)

78-5676 **Reduction of N-Methyl-N′-nitro-N-nitrosoguanidine-induced Mutations by Cobalt Chloride in *Escherichia coli*.** (Eng) Kada, T. (Dept. Induced Mutation, Natl. Inst. Genetics, 1111 Yata, Misima, Sizuoka 411, Japan); Kanematsu, N. *Proc Jpn Acad Ser B Phys Biol Sci* 54(5): 234-237; 1978.

The effect of cobalt chloride on N-methyl-N′-nitro-N-nitrosoguanidine (MNNG)-induced mutations in *Escherichia coli* was investigated. *E. coli* B/r WP2, a strain that requires tryptophan (Try) for growth and reversion to prototrophy, was exposed to 60 μg/ml MNNG for 30 min and then plated on agar that was pretreated with 5-20 μg/ml $CoCl_2$. $CoCl_2$ did not affect the viability of bacteria cells not treated with MNNG and it decreased the number of Try+ colonies per plate considerably, indicating that the compound itself is not mutagenic. With MNNG-treated bacteria, survival decreased slightly with increasing Co concentration, but mutation induction was reduced markedly. The number of Try+ revertants per 10^8 cells decreased from 686.8 without $CoCl_2$ to 640.8 with 5 μg/ml $CoCl_2$ to 10.0 with 20 μg/ml of the compound. Additional experiments showed that the effect of Co was not due to the direct inactivation of MNNG, to inhibition of the expression of Try+ revertants, or to the effects of crowding. It is suggested that $CoCl_2$ blocks an error-prone function induced by the mutagen in a way similar to that occurring in mutagenesis with UV light. (6 refs)

78-5677 **Granuloma Pouch Assay. I. Induction of Ouabain Resistance by MNNG In Vivo.** (Eng) Maier, P. (Inst. Toxicology, Federal Inst. Technology and Univ. Zurich, Schorenstrasse 16, 8603 Schwerzenbach, Swit land); Manser, P.; Zbinden, G. *Mutat Res* 54(2): 159-1 1978.

The granuloma pouch assay was used to test the induc of ouabain resistance to N-methyl-N′-nitro-N-nitrosogu dine (MNNG) in vivo in male albino ZUR:SIV-Z MNNG (0.6 mg) was injected into the sc air pouch 24, and 72 hr after induction of cell growth by croton oil (5 of a 0.25% soln injected sc into the air pouch); and the gra lation tissue was excised 4, 24, and 48 hr later. C bain-resistant cells were demonstrated in all cases ex when MNNG was administered after 48 hr and the tissue excised 4 hr later. The highest mutation frequencies v recorded when MNNG was administered 24 hr after the duction of cell growth and the tissue was excised 48 hr la No ouabain-resistant cells were found when MNNG was ministered po or ip (50 mg/kg) 36 hr after induction of growth and the granulation tissue was excised 36 hr later. data demonstrate that MNNG has mutagenic effects in in mammals if it can interact directly with the target population. (11 refs)

78-5678 **Rapid Detection of DNA Damage by Carc genic Agents Using Immunofluorescence Ultracentrifugation.** (Eng) Neubort, S. (David and Li Coleman Radiology Res. Unit, Dept. Radiology, Albert stein Coll. Medicine, Yeshiva Univ., Bronx, NY, 104 Liebeskind, D.; Leifer, A.; Bases, R. *In: Prevention and tection of Cancer. Proceedings of the Third International S posium on Detection and Prevention of Cancer Held by International Study Group for the Detection and Preven of Cancer in New York, April 26 - May 1, 1976.* Internati Study Group for the Detection and Prevention of Can (New York, NY): Vol. 2(Part 1), 2404 pp.; 2029-2040; 1

The capability of immunofluorescence and ultracentrif tion to detect DNA damage induced by chemical carcino was investigated. In untreated HeLa cell cultures, on small fraction of the cells (≤ 15%) were immunoreacti antinucleoside antibodies. G1 HeLa cells isolated by sele detachment were treated with x-rays (1,000 rads) or chen carcinogens such as N-methyl-N′-nitro-N-nitrosoguani (MNNG: 4 μg/ml for 60 min). Fixed cells were then sta with antinucleoside fluorescent antibodies and observe UV microscopy. The fraction of cells exhibiting nu fluorescence was greatly enhanced by carcinogen treatm When HeLa cells were labeled with ^{3}H-thymidine, g lysed, and sedimented in alkaline sucrose gradients, the D sedimented rapidly as a large macromolecular complex. I treatment with radiation, MNNG, or one of several c carcinogens caused the release of slowly sedimenting gle-stranded DNA. Both methods were MNNG dos pendent. The two approaches yielded similar results fo agents tested, and they were simple, rapid, and sensi Good correlation was generally obtained between the re of the two methods. (21 refs)

679 **The Role of Pre-replication and Post-replication Processes in Mutation Induction in *Haemophilus influenzae* by N-Methyl-N′-nitro-N-nitrosoguanidine.** ;) Kimball, R. F. (Biology Div., Oak Ridge Natl. Lab., Ridge, TN, 37830); Perdue, S. W.; Boling, M. E. *Mutat* 52(1): 57-72; 1978.

repair and fixation of premutational damage induced in *mophilus influenzae* by N-methyl-N′-nitro-N-nitroguanidine (MNNG), were studied with the use of a temture-sensitive DNA elongation mutant (*dna9*) and its binations with mutants defective in pyrimidine dimer exn (*uvrI, uvr2*) and in recombination (*recI*). The *dna9* ant was leaky, allowing about 1% of the normal rate of A synthesis at the restrictive temperature. Repair of nutational lesions was detected by a decline in mutation uency with increasing delay in DNA replication in *dna9* ie restrictive temperature. This repair was unaffected by pyrimidine dimer excision system. Mutation fixation was cted by the ability of DNA from treated and then lysed to transfer mutants to recipient cells by transformation. e fixation occurred at the restrictive temperature, but the unt was much less than that occurring at the nonrestrictemperature, suggesting that an appreciable minority of mutations resulted from lesions introduced near the reation fork but that most mutations arose from lesions inuced at some distance from the fork, perhaps randomly. DNA synthesized immediately after MNNG treatment a lower mol wt than normal DNA, but the mol wt reed to normal with time. This return was blocked in the mutant, suggesting that recombination is involved. (38

5680 **Mutagenesis of S49 Mouse Lymphoma Cells (Meeting Abstract).** (Eng) Coffino, P. (Univ. fornia, San Francisco, CA); Friedrich, U.; Steinberg, R. *at Res* 53(2): 171-172; 1978. (no refs)

5681 **NG-Induced Mutability Within Constitutively Derepressed Histidine Operon of *Salmonella tynurium* (Meeting Abstract).** (Eng) Topisirovic, L. (Lab. ecular Biology, Inst. 'Boris Kidrich', PO Box 522, Belle, Yugoslavia); Krsmanovic-Simic, D. *Mutat Res* 53(2): 1978. (1 ref)

5682 **A Study of the Mutagenic Potential of *N*-Methyl-*N*-Nitro-*N*- Nitrosoguanidine (MNNG) in e by the Translocation Test (Meeting Abstract).** (Eng) genson, T. A. (Stanford Res. Inst., Menlo Park, CA); hbrook, C. J.; Newell, G. W.; Green, S. *Mutat Res* 53(2): -206; 1978. (no refs)

78-5683 **Comparison of Carcinogenicity of N-Alkyl-N′-nitro-N-nitrosoguanidines.** (Eng) Sano, T. (Div. Biochemistry, Natl. Cancer Center Res. Inst., Tsukiji 5-1-1, Chuo-ku, Tokyo 104, Japan); Kawachi, T.; Matsukura, N.; Nakadate, M.; Sugimura, T.; Moriyama, M. *Gann* 69(2): 277-279; 1978.

The carcinogenicity of seven homologs of N-alkyl-N′-nitro-N-nitrosoguanidine, namely, N-methyl-N′-nitro-N-nitrosoguanidine (MNNG), N-propyl-N′-nitro-N-nitrosoguanidine (PrNNG), N-butyl-N′-nitro-N-nitrosoguanidine (BNNG), N-isobutyl -N′- nitro -N- nitrosoguanidine (INNG), N-pentyl -N′- nitro -N- nitrosoguanidine (PeNNG), and N-hexyl -N′- nitro -N- nitrosoguanidine (HNNG), was examined by injecting the compounds sc into male Wistar rats 2x/wk for 5 wk, for a total dose of 85 micromoles. MNNG and /ENNG were strongly carcinogenic; PrNNG, BNNG, and PeNNG also induced tumors at the site of injection, but a lower rate. INNG and HNNG were not carcinogenic. Differences in membrane permeability (due to differences in the length of the alkyl chain), differences in the interaction of the various alkyl groups with nucleic acids, and differences in the repair of the various alkylated DNA's formed in the cell may be related to the differences in carcinogenicity of these compounds. (11 refs)

78-5684 **Effect of Bile Acids and Dietary Fat on Large Bowel Carcinogenesis in Animal Models.** (Eng) Narisawa, T. (Dept. Surgery, Akita Univ. Sch. Medicine, 1-1 Hondo 1-chome, Akita, 010 Japan); Reddy, B. S.; Weisburger, J. H. *Gastroenterol Jpn* 13(3): 206-212; 1978.

The effects of dietary fat and bile acids on chemical carcinogenesis in the large bowel were studied in rats. Female Donryu rats were given an intrarectal dose of N-methyl-N′-nitro-N-nitrosoguanidine (MNNG: 125 mg daily for 4 wk) followed by colostomy (COS) in some rats at 14 or 24 wk. By 60 wk, none of the rats with COS at 14 wk had tumors in the segment distal to the COS; tumors developed in the segment proximal to the COS at the same incidence as that in controls. Animals with COS at 24 wk had tumors in the distal segment, but they were fewer and smaller than those in the controls. Control animals without COS had multiple tumors distributed diffusely in the distal large bowel. The results suggest that luminal contents play a significant role, as cocarcinogens or promotors, in the induction of large bowel cancer. Male and female F344 rats were given a single intrarectal dose of MNNG (4 mg) followed by lithocholic acid or taurodeoxycholic acid (both 1 mg 5x/wk for 11 mo). After 78 weeks, the large bowel tumor incidence of rats treated with MNNG plus bile acid was twice that of rats treated with MNNG alone. Bile acids alone did not produce any tumors. Weanling female F344 rats were fed a diet high or normal in protein and fat. Starting at 7 wk of age, the animals received 1,2-dimethylhydrazine (DMH: 10 mg/kg sc for 20 wk). Ten wk after the last injection, animals fed high pro-

tein-high fat diets had a higher incidence of large bowel tumors than those on the normal diet. The results suggest that a diet high in fat and protein plays a significant role in large bowel carcinogenesis, and they support the concept that colon cancer does not develop, even in the presence of moderate amounts of carcinogen, without the promoting effect of bile acids. (25 refs)

78-5685 **Inhibition of Morphological Transformation Induced with N-Methyl-N′-nitro-N-nitrosoguanidine in Cultures of Hamster Embryo Cells by 5′-Bromo-2′-deoxyuridine-Photolysis.** (Eng) Mironescu, S. G. (Dept. Pathology, Univ. South Carolina, Sch. Medicine, Columbia, SC, 29208). *Int J Cancer* 22(3): 304-314; 1978.

Syrian hamster embryo cells (HEC) were exposed to 5′-bromo-2′-deoxyuridine (BUdR: 3 μg/ml), N-methyl-N′-nitro-N-nitrosoguanidine (MNNG: 0.1-0.5 μg/ml), and fluorescent light (FL: 10-60 min) according to four variants of a protocol termed BUdR-MNNG-photolysis (BMP) to determine whether type III transformed foci induced by MNNG originate from the small subpopulation of cells stimulated by the carcinogen to enter DNA synthesis. Density-inhibited monolayers of HEC were exposed to FL during the last 30 min of the variable treatment periods. Quantitative transformation assays indicated that in nonilluminated cultures, addition of BUdR to MNNG-containing medium affected the transformation frequency of HEC. That is, incidence of type III foci did not subside at later intervals during the post-MNNG administration period as it did in the absence of BUdR. However FL irradiation of HEC treated with MNNG in the presence of BUdR inhibited the development of type III foci markedly. It is possible that BUdR is incorporated into potentially transformed cells during carcinogen-stimulated DNA synthesis and sensitizes them to FL irradiation. The events on which BUdR-induced sensitization of the cells to FL depended took place 5-15 hr after MNNG adminstration; ie, during the period of max carcinogen-stimulated DNA synthesis. FL and/or BUdR were not able to transform HEC. These results provide strong indirect arguments for the concept that carcinogen-induced DNA synthesis and the initiation of transformed clones are causally related. (51 refs)

78-5686 **Factors Influencing the Frequency of Mitomycin C-induced Sister-Chromatid Exchanges in 5-Bromodeoxyuridine-substituted Human Lymphocytes in Culture.** (Eng) Ishii, Y. (Dept. Fundamental Radiology, Faculty Medicine, Osaka Univ., Kita-ku, Osaka 530, Japan); Bender, M. A. *Mutat Res* 51(3): 411-418; 1978.

Possible interactions between 5-bromodeoxyuridine (BUdR, 25 μM) and mitomycin C (MMC, in various concentrations) for the induction of chromosome aberrations and sister chromatid exchanges (SCE's) in cultured human peripheral lymphocytes were studied. MMC induced chromatid ab tions, but there was no indication of synergism bet MMC and BUdR. There was also no evidence of syne between MMC and BUdR for the inducton of SCE's. T ment with MMC starting from the initiation of the phocyte cultures had more effect than treatment only d the last 12 hr of culture, and the SCE yield increased the length of time MMC was present up to 30 hr. MMC-induced DNA lesions persisted long enough so most of those present prior to S phase of the first cell caused additional SCE's in the third cycle. (23 refs)

78-5687 **Induction of Long-Lived Chromosome Da as Manifested by Sister-Chromatid Exch in Lymphocytes of Animals Exposed to Mitomycin-C.** Stetka, D. G. (Biomedical Div., Lawrence Livermore Livermore, CA, 94550); Minkler, J.; Carrano, A. V. *Res* 51(3): 383-396; 1978.

The cytogenetic effects of repeated vs acute exposure to mycin C (MMC, 2 or 4 mg/kg/wk for 1 or 8 wk) were mined using male New Zealand rabbits. The inducti sister chromatid exchanges (SCE's) was determined bromodeoxyuridine-treated cultures of the animals' peri al lymphocytes. MMC increased the SEC frequency 1 day of treatment, the increases being accompanied b creases in the blood concentrations of lymphocytes a creases in the concentrations of neutrophils. The SC quencies returned to intermediate or control levels wi to 3 wk; they remained at these levels in two anima abruptly increased in a third after 42 days. Repeated exp to MMC was at least as effective as acute exposure same total dose in inducing increased SCE's. The mea frequency remained at approx 2 to 2.5 times control until at least day 175 (126 days after the last injection). ered lymphocyte counts and elevated neutrophil cou turned to normal within 3 to 4 wk after the last inj Analysis of lymphocyte SCE's may be an excellent ass determining the results of repeated low-level expos mutagenic/carcinogenic chemicals. (40 refs)

78-5688 **Morphogenesis and Micromorphology o thelial Tumors Induced in the Rat Kidn Nitrosomorpholine. II. Tubular Glycogenesis and the sis of Clear or Acidophilic Cell Tumors.** (Ger) Bannas (Abteilung fur Cytopathologie, Institut fur experim Pathologie, Deutschen Krebsforschungszentrum Heid Im Neuenheimer Feld 280, D-6900 Heidelberg 1, W many); Krech, R.; Zerban, H. *Z Krebsforsch* 92(1): 1978.

Light and electron microscopy was used to study the de ment of clear and acidophilic (granular) cell kidney t in Sprague-Dawley rats given 12 or 50 mg/100 ml trosomorpholine (NNM) in their drinking water for 3-

he end of treatment, the kidneys were morphologically lar to those of control rats. Some weeks later, however, ssive amounts of glycogen (glycogenesis: GGOS) were d stored in single tubules. After a lag period of 22-97 wk, lar GGOS affected > 50% of the rats, and clear and/or ophilic cell kidney tumors developed in 25%-30%. Vari- intermediate stages between GGOS (which occurred as as 3 wk after withdrawal of NNM) and tumors were d, which indicates that the former is a preneoplastic le- In addition to clear cells, the tumors contained predomi- ly cells that stored lipids or were rich in mitochondria). The tumor ultrastructure pointed to the differentiated l tubules as the target tissue. The glycogen of the clear was located preferentially in the cytoplasm, but it was found enclosed in autophagic vacuoles. The lipids ied membranous cytoplasmic bodies with a regular pat- of dark and light lines. The MC of the tumor cells, espe- y the acidophilic cells, were often characterized by a ked reduction in cristae. Large MC lacking in cristae but an abundant matrix were sometimes found. Interstitial rich in acid mucopolysaccharides were distributed loose- roughout the clear cell tumors. It is suggested that the OS, lipidosis, and mucopolysaccharidosis signify a dis- ance of the cellular metabolism that might be closely cor- ed with carcinogenesis. (48 refs)

5689 **Morphogenesis and Micromorphology of Epithelial Tumors Induced in the Rat Kidney by osomorpholine. III. Oncocytic Tubules and On-** ytomas. (Ger) Bannasch, P. (Abteilung fur Cytopatho- e, Institut fur experimentelle Pathologie, Deutschen bsforschungszentrum Heidelberg, Im Neuenheimer d 280, D-6900 Heidelberg 1, W. Germany); Krech, Zerban, H. *Z. Krebsforsch* 92(1): 87-104; 1978.

gue-Dawley rats were given 12 or 50 mg/100 ml itrosomorpholine in their drinking water for 3-14 wk, and development of renal oncocytomas was followed by light electron microscopy. At the end of treatment, the kid- s were morphologically similar to those of control rats; vever, some weeks later, oncocytic (OC) transformation ubular epithelia and other tubular lesions were common. tal and OC tubular segments were often directly connect- OC tubules were present in 66% of the rats after a lag iod of 22-97 wk. OC microadenomas originated from these tubules and developed in 36% of the rats during this period. Approx 20% of the control rats had single OC tubules and 6% had microadenomas. In some tubules, the oncocytes were combined with cells that stored excessive amounts of glycogen or lipids. Mitochondria rich in cristae and with diverse structural anomalies accumulated in the cytoplasm. In some mitochondria, the cristae were aligned in parallel and were connected by cross bridges 15-20 nanometers wide. Intramitochondrial aggregates of glycogen surrounded by a single membrane were noted, along with vesicles of the endoplasmic reticulum, Golgi complexes, and lipid bodies with a regular pattern of dark and light lines. Numerous glycogen particles were found in the cytoplasm of some oncocytes. A few of these cells showed a homogeneously condensed nucleus and cytoplasm. Interstitial cells rich in mucopolysaccharides were often found between the oncocytes. The oncocyte is suggested to be a special type of neoplastically transformed cell. (35 refs)

See also:
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*(Phys.): 78-5694, 78-5695, 78-5697, 78-5699, 78-5700, 78-5701, 78-5702, 78-5708, 78-5721, 78-5730.
*(Viral): 78-5758, 78-5808, 78-5810, 78-5847.
*(Immun.): 78-5857, 78-5861, 78-5866, 78-5867.
*(Path.): 78-5873, 78-5874, 78-5876, 78-5878, 78-5888, 78-5890, 78-5894, 78-5895, 78-5896, 78-5898.
*(Epid.-Biom.): 78-5922, 78-5926, 78-5929, 79-5931, 78-5932, 78-5937, 79-5938, 78-5939, 78-5940, 78-5952, 78-5954, 78-5959, 78-5960, 78-5964, 78-5967, 78-5968, 78-5969, 78-5971.

78-5690 **The Proliferative Status and Clonogenic Capacity of Tumor Cells in a Transplantable Rhabdomyosarcoma of the Rat Before and After Irradiation with 800 Rad of X-rays.** (Eng) Hermens, A. F. (Radiobiological Inst. TNO, 151 Lange Kleiweg, Rijswijk, The Netherlands); Barendsen, G. W. *Cell Tissue Kinet* 11(1): 83-100; 1978.

R-1 rhabdomyosarcomas transplantable in the inbred strain of WAG/Rij rats were labeled semicontinuously with (^{3}H)-thymidine (^{3}H-TdR) and subsequently irradiated with x-rays to estimate the rate of recruitment of nonproliferative cells (Q) into the proliferative cells (P). Animals received up to seven ip injections of ^{3}H-TdR (0.5 μCi/g of body wt) within 30 hr and half of the tumors received an acute dose of 800 rad of 300 kV x-rays 45 min after the completion of the last labeling in order to reduce the fraction of well-oxygenated cells to $<1\%$ of the surviving clonogenic cells. Analysis of the variation in the fraction of labeled tumor cells as a function of time and of the number of injections showed that the rate of recruitment of Q cells into P cells was $<1\%$/hr. Comparison of data on the fractions of labeled cell foci derived for irradiated and nonirradiated tumors indicated that clonogenic Q cells were more frequently present among cells which survived the irradiation. These results suggest that in R-1 tumors of approx 800 mm^3 the clonogenic Q cell population contains a larger fraction of hypoxic cells than the clonogenic P cell population. It was also demonstrated that in vitro cultured cells isolated from in vivo labeled tumors did not reutilize breakdown products of ^{3}H-labeled DNA to an extent which would significantly influence values derived for fractions of foci originating from labeled P cells. (25 refs)

78-5691 **Sensitivity of Human Lymphocytes to Radiation During Various Phases of the Cell Cycle.** (Rus) Kukushkina, L. M. (Inst. Genetics and Cytology, Minsk, USSR); Mikhalevich, L. S. *Dokl Akad Nauk BSSR* 22(4): 371-374; 1978.

To evaluate the radiosensitivity of cells in various phases of the cycle, human lymphocyte cultures were treated with phytohemagglutinin (PHA) and, 1-50 hr later, with x-rays (100 R). The yield of chromosome aberrations in cells irradiated 46 and 50 hr after treatment with PHA was max, 77.8% and 83.0%, respectively, vs 66.6% in cells irradiated 20 hr and 40.0% in cells irradiated 1 hr after treatment. (10 refs)

78-5692 **Mitotic Cycle and Production of Chromosome Structural Changes in Human Cells (Meeting Abstract).** (Eng) Luchnik, N. (Inst. Medical Radio Acad. Medical Sciences USSR, Obninsk 249020, Di Kaluga, USSR). *Mutat Res* 53(2): 224; 1978. (no refs)

78-5693 **Gene Mutation Systems in Mammals (Me Abstract).** (Eng) Malling, H. V. (Lab. Env mental Mutagenesis, Natl. Inst. Environmental H Sciences, P.O. Box 12233, Research Triangle Park, 27709); Valcovic, L. R. *Mutat Res* 53(2): 227; 1978. (no

78-5694 **Studies on the Relationship Between SCE Chromatid Aberrations in Endoredupli Cells (Meeting Abstract).** (Eng) Palitti, F. (Centro di S di Genetica Evoluzionistica, CNR, Universita di R Rome, Italy); Becchetti, A.; Perticone, P.; Diana, G. *Res* 53(2): 247; 1978. (2 refs)

78-5695 **Non-disjunction Induction by Muta Agents in Male Cells of the Northern Vol *crotus oeconomus* (Meeting Abstract).** (Eng) Tates, (Dept. Radiation Genetics and Chemical Mutagenesis, Leiden, Leiden, Netherlands). *Mutat Res* 53(2): 27 1978. (1 ref)

78-5696 **Does the Capacity to Rejoin Radiation-in DNA Breaks Decline in Senescent Mice?** Ono, T. (Dept. Radiation Biophysics, Faculty Med Univ. Tokyo, Tokyo, Japan); Okada, S. *Int J Radia* 33(4): 403-407; 1978.

The rejoining rates of radiation-induced DNA scissions livers of 2-, 14-, and 22-mo-old C57BL/6 mice and i cerebellums of 2- and 22-mo-old mice were compared. S strand breaks induced in the DNA of the cerebellum krad were rejoined at a similar rate in both 2- and 22-m mice. There was a half-time of 2 hr; after this time, th centage of breaks remained at 15%-20% for up to 2 Radiation-induced single-strand scissions of DNA in th were also repaired quickly, with a half time of 1.2 2-mo-old mice and 1.3 hr in 14- and 22-mo-old mice. H er, the size of the slow or nonrejoinable fraction in the mice was very difficult to estimate because of the freq and experimental variation of the inherent age-asso DNA breaks in the livers of old mice (31%-47% of the radiation-induced breaks). The results indicate tha hepatic cells of old mice were able to rejoin radiation-in

scissions as quickly as those of young mice, but that ge-associated DNA scissions could not be rejoined. (22

697 **Unrepaired Single and Double DNA Strand Breaks Shown Cytogenetically Following X-ir-tion of Lymphocytes from Patients with Ataxia Telan-asia (Meeting Abstract).** (Eng) Taylor, A. M. (Dept. er Studies, Medical Sch., Birmingham B15 2TJ, En-l). *Mutat Res* 53(2): 274; 1978. (1 ref)

698 **Ozone, UV Light, Sunbathing, and Skin Cancer (Letter to Editor).** (Dan) Thorling, E. B. (Kra-rskningsinstituttet, Aarhus, Denmark). *Ugeskr Laeg* 38): 2316-2317; 1978.

surements of atmospheric ozone levels have failed to give istent results, which may be due to the use of different suring techniques. Measurements performed in Denmark shown no noteworthy change during the last 12 years, other measurements indicated that current ozone levels 20% lower than 1951 levels. In view of the skin can-nducing effect of UV radiation, any reduction of the e level, which increases the intensity of UV radiation, have serious consequences. (6 refs)

699 **Protection Against Nitrosoguanidine or UV-Radiation Lethality by Streptomycin in Cyanophytes (Meeting Abstract).** (Eng) Sinha, B. D. ot. Botany, Univ. Bihar, Muzaffarpur 842001, India); har, H. D. *Mutat Res* 53(2): 263-264; 1978. (no refs)

5700 **The Isolation and Characterisation of a Dam-age-dependent Endonuclease from *Micrococcus eus* (Meeting Abstract)** (Eng) Riazuddin, S. (Dept. Bio-nistry, Johns Hopkins Univ., 615 N. Wolfe St., Bal-ore, MD, 21205); Grossman, L. *Mutat Res* 53(2): 252-253; 3. (no refs)

5701 **Mutation Studies with *Micrococcus radiodurans* Auxotrophs: Effects of Exposure to Radiation, micals, and Combined Radiation/Chemical Treatment eting Abstract).** (Eng) MacPhee, D. G. (Dept. Genetics, Trobe Univ., Bundoora, Victoria 3083, Australia); Kami-Sarbinowsky, M. *Mutat Res* 53(2): 238-239; 1978. (no refs)

5702 **Mutagenicity of 8-Methoxy-psoralen and Long-Wave Ultraviolet Irradiation (Meeting Abstract).** (Eng) Simmons, J. W. (Dept. Radiation Genetics and Chemical Mutagenesis, State Univ. Leiden, Leiden, Netherlands); Burger, P. M. *Mutat Res* 53(2): 263; 1978. (no refs)

78-5703 **Chromosomes after Psoralen/UVA Treatment In Vitro and In Vivo (Psoriasis Patients) (Meeting Abstract).** (Eng) Brogger, A. (Genetics Lab., Norsk Hydro's Inst. Cancer Res., Montebello, Oslo, Norway); Waksvik, H.; Thune, P. *Mutat Res* 53(2): 157-158; 1978. (no refs)

78-5704 **Lack of Cytotoxicity and Mutagenicity of Ultraviolet Radiation in Normal Diploid Human Fibroblasts as Contrasted with Cells Deficient in DNA Repair (Meeting Abstract).** (Eng) Maher, V. M. (Michigan State Univ., East Lansing, MI, 48824); McCormick, J. J. *Mutat Res* 53(2): 225-226; 1978. (no refs)

78-5705 **Photoreactivation of Pyrimidine Dimers in Human Cells (Meeting Abstract).** (Eng) Mortelmans, K. (Stanford Res. Inst., Menlo Park, CA); Friedberg, E. C.; Brorsson, M. *Mutat Res* 53(2): 234; 1978. (2 refs)

78-5706 **Co-operative Denaturing Effect of Heat and UV on DNA in Human Squamous Cells (Meeting Abstract).** (Eng) Roth, D. (Inst. Environmental Medicine, New York Univ., New York, NY). *Mutat Res* 53(2): 254-255; 1978. (no refs)

78-5707 **Technical and Theoretical Considerations in Evaluating Individual Variations in Human Unscheduled DNA Synthesis (UDS) (Meeting Abstract).** (Eng) Delozier, D. (Dept. Medical Genetics, Indiana Univ. and Methodist Hosp., Indianapolis, IN); Antley, R. *Mutat Res* 53(2): 176-177; 1978. (no refs)

78-5708 **Synergistic Interaction of Hydrogen Peroxide and Near-Ultraviolet Radiation (Meeting Abstract).** (Eng) Eisenstark, A. (Div. Biological Sciences, Univ. Missouri, Columbia, MO); Ananthaswamy, H. N.; Hartman, P. S. *Mutat Res* 53(2): 184; 1978. (no refs)

78-5709 **The Kinetics of Thymine Dimer Excision in Ultraviolet-irradiated Human Cells.** (Eng) Ehmann, U. K. (Lab. Experimental Oncology, Dept. Pathology,

Stanford Univ. Sch. Medicine, Stanford, CA, 94305); Cook, K. H.; Friedberg, E. C. *Biophys J* 22(2): 249-264; 1978.

The kinetics of thymine dimer loss from the acid-insoluble fraction of UV-irradiated human fibroblast cells was investigated, and the findings were compared with data on repair synthesis. UV fluences of 10-40 joules/m^2 produced an av of 21-85 x 10^5 thymine dimers per cell and an eventual maximal loss per cell of 12-20 x 10^5 thymine dimers. The time for half-maximal loss of dimers ranged from 12 to 22 hr after UV irradiation. In contrast, the time for half-maximal repair synthesis of DNA measured by autoradiography was 4.5 hr. This figure is in good agreement with reported half-maximal repair synthesis times, which range from 0.5 to 3.6 hr. The discrepancy in the kinetics of the loss of thymine dimers from DNA and repair synthesis may be explained by one of the following: (1) the loss of thymine dimers from the DNA was not equated with thymine dimer excision, because it is possible that pyrimidine dimers are excised as acid-precipitable oligonucleotides that are then reduced to acid-soluble products by enzymatic degradation; (2) the different treatment of the cells inherent in the techniques used in measurement of repair synthesis and dimer excision; (3) repair synthesis may not reflect pyrimidine dimer excision in mammalian cells, and (4) the rapid kinetics of repair synthesis compared with the slower loss of thymine dimers may reflect a patch and cut-type mechanism in which repair synthesis occurs before the enzymatic removal of the dimers. (58 refs)

78-5710 **Cancer of the Colon as a Late Sequel of Pelvic Irradiation.** (Eng) Greenwald, R. (Dept. Medicine, Div. Gastroenterology, Univ. Miami Sch. Medicine, P.O.B. 520875 Biscayne Annex, Miami, FL, 33152); Barkin, J. S.; Hensley, G. T.; Kalser, M. H. *Am J Gastroenterol* 69(2): 196-198; 1978.

A 36-yr old woman developed a carcinoma of the rectum 9 yr after therapeutic radiation for a pelvic malignancy. Prolonged follow-up is urged for 5-yr survivors of pelvic irradiation, since the symptoms of radiation-induced proctocolitis may mimic those of carcinoma of the colon and rectum. (7 refs)

78-5711 **Fibrosarcoma in a Previously Irradiated Larynx.** (Eng) Donaldson, I. (Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL, England). *J Laryngol Otol* 92(5): 425-428; 1978.

A 68 yr-old man developed a laryngeal tumor at a site that had been treated by radiotherapy for a squamous cell carcinoma. The patient had received a tumor dose of 5,600 R delivered in 12 treatments 11 yr previously. It is suggested that the neoplasm was induced by the radiation. (18 refs)

78-5712 **Parathyroid Adenoma and Prev Head-and-Neck Irradiation.** (Eng) Schacl S. H. (Fairfax Hosp., Falls Church, VA); Hall, A. *Ann I Med* 88(6): 804; 1978.

The occurrence of a parathyroid adenoma in a 48-yr-old and a 35-yr-old woman who had previously been treated head and neck radiation is reported. The man had bee radiated extensively for facial acne at age 23, and the wo had received radiation therapy for thymic enlargement infant and later for acne. (5 refs)

78-5713 **Sensitivity of the Thyroid and Parath Glands to Radiation.** (Eng) Clark, O. H. (S cal Service (112), Veterans Admin. Hosp., 4150 Clemen San Francisco, CA, 94121); Rollo, D.; Stroop, J.; Cas B.; Rehfeld, S. J.; Loken, H. F.; Deftos, L. J. *J Surg Res* 2 374-379; 1978.

The effect of radiation on male Sprague-Dawley rat th and parathyroid glands, the sensitivity of thyroid folli and parafollicular cells to this radiation, and the effe thyroid-stimulating hormone (TSH) on the sensitivity gland to radiation were determined. All animals were tr by hemiparathyroidectomy and hemithyroidectomy; ha animals had a ^{125}I seed implanted next to the remaining t All animals were then placed on one of three diets low-iodine diet (LID) and deionized water, (2) lab chow tap water, (3) lab chow and L-sodium thyroxine 6 μg/100 g/day) in the drinking water. Blood ples were obtained at 4 and 10 wk; at 10 wk, all were removed and the animals placed on lab chow Blood samples were taken again 2, 4, and 9 wk and the animals were sacrificed. ^{125}I seeds selec inhibited thyroid function compared with parath function. Stimulation of thyroid tissue by TSH suppression of this tissue by T_4 did not alter its sitivity to radiation, since serum TSH concentra were not different in the T_4-suppressed, control TSH-stimulated animals 9 wk after the radiation was di tinued. TSH stimulation by the LID and TSH suppre by exogenous T_4 did alter the function of the parafolli C cells, since serum calcitonin concentrations were incr with the former treatment and decreased with the l Serum Ca concentrations were also increased in the LID but the reason for this increase is not known. (23 refs)

78-5714 **Irradiation-induced Polyglandular Neoplas the Head and Neck.** (Eng) Swelstad, J. A. Surgical Oncology, Northwestern Univ. Medical Ce Evanston, IL, 60201); Scanlon, E. F.; Oviedo, M. A.; H N. E. *Am J Surg* 135(6): 820-824; 1978.

The occurrence of 13 salivary gland tumors and 8 thyroid adenomas in 18 patients with a history of radiot py to the head and neck is reported. Nine of these pat

had thyroid neoplasms, 37% of which were malignant 37% of which showed some degree of radiation thyroidi- The salivary gland tumors and thyroid nodules were often covered simultaneously in the same patient. Nine of the salivary gland tumors were of parotid origin. All three ior salivary gland tumors and six of the parotid tumors e malignant. The latent period for the salivary tumors raged 30 yr between irradiation and diagnosis. Of the it patients with parathyroid adenomas, one had three erplastic parathyroid glands and seven had single adeno- s. The latent period for the adenomas averaged 27 yr. All it patients remained normocalcemic after surgical man- ment, although the presurgical hypercalcemia in four was iptomatic. Examination of the salivary glands and thyroid ecommended for patients with a history of radiation to head and neck. (10 refs)

-5715 **Radiation-induced Cancer of the Thyroid.** (Eng) Sonenberg, M. (Endocrinology Service, Dept. dicine, Memorial Sloan-Kettering Cancer Center, New rk, NY); Leeper, R. D. *Clin Bull* 8(1): 29-33; 1978.

ong 64 persons with a history of head and neck radiation, pable thyroid abnormalities were found in 5/11 irradiated acne, 2/12 for hemangioma, 1/9 for adenoids, and 4/11 miscellaneous reasons. None of 21 patients treated for an arged thymus had abnormalities. The thyroid in the acne up ranged from 0.5 to 2 cm. (12 refs)

-5716 **Radioiodine Treated Hyperthyroidism and Thyroid Carcinoma.** (Eng) Appell, R. (Dept. Surg-, George Washington Univ. Medical Center, 2150 Pennlvania Ave., N.W., Washington, DC, 20037); Tsangaris, ; Spiegel, J. *Am Surg* 44(8): 537-540; 1978.

papillary thyroid carcinoma developed 4 yr after radioac- e iodine therapy for hyperthyroidism in a 48-yr-old wom- . Statistics on 14 similar literature cases are tabulated. (22 fs)

-5717 **A Nine-Year Cytogenetic Follow-up of a Patient Injected with Thorotrast.** (Eng) Ishihara, T. Div. Radiation Health, Natl. Inst. Radiological Sciences, hiba 280, Japan); Kohno, S.; Hayata, I.; Kumatori, T. *Hum enet* 42(1): 99-108; 1978.

62-yr-old man who had been given > 15 ml Thorotrast in 1939 was subjected to cytogenetic follow-up for 9 yr efore his death in 1974. No malignancy resulted, but there as extensive Thorotrast deposition in the liver and several mph nodes. The estimated doses of radiation absorbed by ver, spleen, and bone marrow were 32, 653, and 4 rad/yr, espectively. Both Cu (dicentrics, rings, and acentric fragments) and Cs (reciprocal translocations, inversions, deletions, duplications) types of chromosomal abnormalities were observed in the peripheral T lymphocytes at frequencies of 4.5%-9.0% and 6.0-11%, respectively, throughout the follow-up period. All of the chromosomal abnormalities in the bone marrow cells were of the Cs type, and they ranged in frequency from 2.17% to 5.4% during the first three samplings. An increase in frequency (up to 26%) at the last sampling was mainly due to cells lacking a Y chromosome (19% of all cells). The 50 aberrant bone marrow cells analyzed consisted primarily of cells lacking a Y chromosome (19 cells) and cells of clone A (25). Fifteen of the cells lacking a Y chromosome possessed an additional reciprocal translocation involving chromosomes 12 and 17. Clone A cells were observed an av frequency of about 4%. The karyotypes of clone A cells from the bone marrow and peripheral lymphocytes were identical, involving translocation of part of the short arm of chromosome 2 onto the short arm of 22. Clone B occurred in the peripheral lymphocytes at an av frequency of 0.43%; it was also identified in one bone marrow cell. Cells lacking a Y chromosome were not identified in the peripheral lymphocytes. The finding of Clone A suggests the existence of a genetic factor related to the development of chronic myelocytic leukemia. (27 refs)

78-5718 **Thyroid Cancer Risk from Iodine-131 Treatment?** (Ger) Creutzig, H. (Department fur Radiologie, Medizinische Hochschule, Postfach 610 180, D-3000 Hannover 61, W. Germany); Hundeshagen, H. *Med Klin* 72(19): 855-857; 1977.

The case histories of 240 thyroid carcinoma patients revealed that 5 had ^{131}I treatment for benign thyroid diseases 0.5-5 yr before the diagnosis of carcinoma and 1 had x-irradiation of the thyroid gland 30 yr before the appearance of carcinoma. For comparison, the prevalence of thyroid carcinoma in a region without endemic goiter was found to be 2% to 5%. The findings indicate that there is no relationship between the incidence of clinically manifest thyroid carcinoma and ^{131}I therapy. (17 refs)

78-5719 **Occupational Exposure to Ionising Radiation: The Risk in Perspective.** (Eng) Bonnell, J. A. (Nuclear Health and Safety Dept., Central Electricity Governing Board, London, England); Harte, G. *Lancet* 1(8072): 1032-1034; 1978.

The risk of somatic and genetic disease incurred by exposure to ionizing radiation was calculated using the International Commission on Radiological Protection risk factors and a simple risk-time relationship. For an individual exposed at 10 millisieverts (mSv)/yr from age 20, the risk of death from radiation-induced leukemia is between 1 in 100,000 and 1 in 50,000. (One sievert equals 100 rem.) If the worker has children at age 40, the risk of a serious genetic disease in his

descendants is 1 in 500 for the first two generations and 1 in 250 for subsequent generations. If a person is exposed from birth to 1 mSv/yr from nuclear plant operations and he receives a total of 25 mSv by age 25, the risk of genetic disease in his descendants will be 1 in 2,000. (8 refs)

78-5720 **Occupational Exposure to Ionising Radiation (3 Letters to Editor).** (Eng) Lindop, P. J. (Dept. Radiobiology, Medical Coll. St. Bartholomew's Hosp., London EC1M 6BQ, England); Mole, R. H.; Reissland, J. A.; Dolphin, G. W. *Lancet* 1(8074): 1155-1157; 1978.

A previous paper indicated that an individual exposed to 10 milliSieverts (1 Sievert = 100 rem) from age 20 incurs a risk of death from radiation-induced leukemia of 1 in 100,000 to 1 in 50,000. This is actually the annual risk; the total risk is 1 in 4,000. Expert testimony on the effects of occupational exposure to radiation on cancer incidence is challenged. Finally, the results of a study of cancer incidence in Portsmouth Naval Shipyard workers should not be cited as fact because of the incompleteness of the data and the uncertainty in the categorization of radiation and nonradiation workers. (5 refs)

78-5721 **Low Dose-Rate Experiment with Tritiated Thymidine as a Simulator of Chemical Mutagens Using Silkworm Oocyte System (Meeting Abstract).** (Eng) Tazima, Y. (Natl. Inst. Genetics, Misima, Japan). *Mutat Res* 53(2): 274-275; 1978. (no refs)

78-5722 **Effects of Whole-Body Irradiation on Neonatally Thymectomized Mice: Incidence of Benign and Malignant Tumors.** (Eng) Anderson, R. E. (Dept. Pathology, Univ. New Mexico Sch. Medicine, Albuquerque, NM, 87131); Howarth, J. L.; Troup, G. M. *Am J Pathol* 91(2): 217-228; 1978.

The individual and cumulative effects of neonatal thymectomy (nTx) and irradiation on benign and malignant tumor incidence were determined in germ-free Charles River mice. The mice underwent either thymectomy or sham thymectomy (STx) within 24 hr of birth; at 6 wk of age, mice from both groups were exposed to 700 rads' whole-body irradiation. nTx increased the incidence of benign and malignant tumors and the prevalence of multiple primary neoplasms in individual mice, but it had no effect on the latent period. Irradiation further increased the incidence of benign and malignant tumors in both groups, but the increment was much more pronounced the STx mice than the nTx mice. In addition, irradiation accelerated the appearance of these tumors in both groups, but the effect was more pronounced in STx mice. Thus, the cumulative effects of thymectomy plus irradiation were less pronounced than the sum of the individual effects. Some of the carcinogenic effects of whole-body irradiation may be mediated by suppressio the thymic-dependent component of the immune system refs)

78-5723 **Rat Skin Tumor Incidence Following Single Fractionated Exposures to Proton Radia** (Eng) Burns, F. J. (Inst. Environmental Medicine, New Univ. Medical Center, New York, NY, 10016); Strickl P.; Vanderlaan, M.; Albert, R. E. *Radiat Res* 74(1): 152- 1978.

The dose-response curve and degree of split-dose recover tumor induction and hair follicle survival were determ in male albino CD rat skin irradiated with protons. A pr beam from a cyclotron was modified to provide an ap linear decrease in dose with depth in tissue to a max of a 1.3 mm. Six doses were given in the range 75-750 rads. tumor yield at 100 wk postirradiation increased as 2.8 D (dose). Split doses consisted of an initial dose of 150 followed 24 hr later by graded doses in the range 150 rads. Split doses produced a sparing effect on follicle ki and on yield of tumors. The magnitude of the reductio tumor yield was consistent with complete recovery. Com sons with previous results indicated that protons were 2.(times as effective as electrons for tumor induction and the shapes of the dose-response curves were generally sim (11 refs)

78-5724 **Reactions of Radicals with Lecithin Bila** (Eng) Barber, D. J. (Chemistry Dept., U Notre Dame, Notre Dame, IN, 46556); Thomas, J. K. *Re Res* 74(1): 51-65; 1978.

The reaction rates of hydroxyl radicals (OH) and the hy ed electron e(aq)- with lecithin bilayers were determined. rate for OH + lecithin was $5.1 \pm 0.9 \times 10^8$/M that for e(aq)- + lecithin was very slow. With py in lecithin, the reaction rates for OH and e(aq)- $1.65 \pm 0.12 \times 10^9$ and 7×10^7/m/sec, respecti These rates were lower than those observed for sir reactions in homogeneous soln. The differ is attributable to the protective effect of the bil and to the restricted diffusion imposed on the reactive spe by the bilayer. Long-term alteration in the model memb following OH attack is manifested by damage to the l group (which increases the water penetration of the bila and by cross-linking within the membrane (which resti motion in the bilayer interior). These results are relevant studies of the effects of low linear-energy-transfer radia on biological membranes. (27 refs)

78-5725 **Chromosome Aberrations Induced in Hu Lymphocytes by Radiation from ^{252}Cf.** (I Lloyd, D. C. (Natl. Radiological Protection Board, Harv

ot, Oxfordshire OX11 ORQ, England); Purrott, R. J.; er, E. J.; Edwards, A. A.; Dolphin, G. W. *Int J Radiat* 34(2): 177-186; 1978.

induction of chromosome aberrations in lymphocytes a healthy adult male by ^{252}californium (Cf) neutron tion was studied and compared with aberration induc- by other types of radiation. An analysis of the dose-effect e in which the dose (D) of Cf neutrons was related to ield (Y) of neutron-induced dicentric aberrations re- d that for the two highest energy neutron curves (7.6 4.7 million electron volts), the best fit was obtained with ear-quadratic expression in which Y was a function of us D^2. For lower energy neutron curves, the best fit was ned with a simple linear expression in which Y was a ion of D. The relative biological effectiveness (RBE) for with respect to ^{60}cobalt was about 27 at very low doses, easing to 6 at an aberration Y equivalent to 400 rads of ads/hr gamma radiation. A profile of chromosome aber- n induction with depth was obtained by placing blood ples at distances of 0.65-2.05 cm from the Cf source. The of Cf radiation relative to ^{226}radium gamma radiation eased with distance from the source and more than dou- over the distance range. This increasing RBE indicates Cf is more effective at a greater distance in producing omosome aberrations and, presumably, in destroying the ty of cells to divide. This effect may be an advantage in treatment of large tumors. (16 refs)

5726 **Metabolism and Microdistribution of Californium-252 and Its Effects on Pulmonary Parenma During Intratracheal Administration to Rats.** (Rus) rova, E. S. (No affiliation given.); Stepanov, S. V. *Radiologiia* 18(5): 724-729; 1978.

dom-bred albino rats were given a single intratracheal of californium-252 (0.016, 0.004, or 0.0005 μCi/g). hin 1-600 days of exposure, the rats were sacrificed and specimens were studied histologically and radiometri- y. Structural changes in the bronchial epithelium and in endothelium of the vessels (karyopyknosis, vacuolization, desquamation) were seen on days 7-14 after Cf252 administration (rats treated with 0.016 μCi/g also showed dection of their alveolar epithelium). Starting from days 30, and 210, rats treated with 0.016, 0.004, and 0.0005 μCi/g, ectively, had sclerotic changes in the lung tissue, hyperia of the bronchial and alveolar epithelium, and metaia of the columnar epithelium. Of six rats who were exed to 0.0005 μCi/g and survived 600 days, four developed g tumors (1 adenocarcinoma, 2 squamous cell carcinomas, acrofollicular lymphoblastoma). (3 refs)

5727 **Effect of Combined Alginate Treatments on the Distribution and Excretion of an Old Radiostium Contamination.** (Eng) Vanderborght, O. L. (Mineral Metabolism Lab., Radiobiology Dept., Belgian Nuclear Centre, S.C.K./C.E.N., B 2400 Mol, Belgium); Van Puymbroeck, S.; Babakova, I. *Health Phys* 35(2): 255-258; 1978.

Mobilization of ^{85}Sr from the skeleton was studied in mice through combined treatment with sodium alginate incorporated in a dough plus alginate injected ip as an aqueous solution. Two-month-old C57 Black male mice were injected ip with 40 μCi $^{85}SrCl_2$. After 9 wk, mice were divided into five experimental groups: 1 was fed alginate dough containing 100 g sodium alginate and injected with NaCl; 2 was fed alginate dough and injected ip with 2 mg sodium alginate 2x/day; 3 was fed agar dough and injected with NaCl; 4 was fed agar dough and injected with sodium alginate; 5 was fed standard pellets and injected with NaCl. Treatment lasted 3 days during which urine and excreta were collected and analyzed for ^{85}Sr content. After the 3 days, mice were killed and ^{85}Sr content of blood, liver, spleen, kidney, and femur was determined. Levels in blood, liver and kidney increased when either alginate dough or injection was given; excretion in the feces was increased in mice fed alginate; and excretion in the urine increased in mice injected with alginate. Mice in group 2 had a significantly high increase in ^{85}Sr in blood without an equivalent increase in fecal ^{85}Sr, indicating that the ^{85}Sr mobilized by injected alginate was not fully available for intestinal excretion. However, about half the ^{85}Sr mobilized in the blood by alginate injection was available for renal excretion. Combined treatment overcame the decrease in urinary ^{85}Sr excretion obtained with alginate in diet only. The radionuclide content of liver, kidney, and spleen was increased four- to six-fold by the combined treatment. (9 refs)

78-5728 **Antigenicity of ^{90}Sr Induced Tumors (2 Letters to Editor).** (Eng) Nilsson, A. (Dept. Pathology, Coll. Veterinary Medicine, Swedish Univ. Agricultural Sciences, S-750 07 Uppsala, Sweden); Revesz, L.; Larsson, S. E.; Lorentzon, R.; Boquist, L. *Acta Pathol Microbiol Scand (A)* 86(4): 331-332; 1978.

Facts underlining the difficulties of interpreting and comparing two studies of the immunostimulating effect of BCG on ^{90}Sr-induced osteosarcomas are given. Factors such as time of BCG treatment, ^{90}Sr dose, and duration of animal survival differed between the two and affected tumor incidence. (4 refs)

78-5729 **Radium-induced Malignant Tumors of the Mastoid and Paranasal Sinuses.** (Eng) Littman, M. S. (Center Human Radiobiology, Argonne Natl. Lab., Argonne, IL, 60439); Kirsh, I. E.; Keane, A. T. *Am J Roentgenol* 131(5): 773-785; 1978.

A survey of records kept at the Center for Human Radiobiology (Argonne National Laboratory, Argonne, IL) revealed 21 patients with mastoid carcinoma (MC) and 11 with malig-

nant paranasal sinus tumors (PST) among 5,058 persons occupationally or therapeutically exposed to radium. People were exposed via the luminous watch-dial industry, the industrial and research processing of Ra, and medical treatment. Most of the patients (28) were women employed in the dial-painting industry. The four men received Ra therapeutically. Tumor induction times were 21-50 yr for the MC (median, 33) and 19-52 yr for the PST (median, 34). Of the 27 patients whose body burdens of Ra were measured, the calculated skeletal dose ranged from 605 to 19,519 rads; 25 of these patients had skeletal doses > 1,000 rads. Of the total 2,036 persons (including the 27 patients) whose Ra body burdens were measured, 200 had a skeletal dose > 1,000 rads; the frequency of the two cancers among the latter was relatively constant with dose and averaged 13%. There was a high proportion of mucoepidermoid carcinoma, comprising 38% of the MC and 36% of the PST. Three patients had antecedent bone sarcoma at 20, 11 and 5 yr, respectively, and a bone sarcoma was discovered at autopsy in a fourth patient. Radiographic changes in the mastoid and paranasal sinuses were similar to those in non-Ra malignant tumors. More than 800 persons exposed to Ra before 1930 and another group of unknown size who received Ra therapeutically are still at risk of developing MC and PST. (46 refs)

78-5730 **Carcinogenesis in Tissue Culture. 29: Neoplastic Transformation of a Normal Human Diploid Cell Strain, WI-38, with Co-60 Gamma Rays.** (Eng) Namba, M. (Dept. Pathology, Kawasaki Medical Sch., Kurashiki 701-01, Japan); Nishitani, K.; Kimoto, T. *Jpn J Exp Med* 48(4): 303-311; 1978.

Neoplastic transformation of a normal human diploid cell strain, WI-38, by irradiation with ^{60}Co γ-rays is described. In preliminary studies, a series of potentially carcinogenic agents was tested for transforming ability with human lymphocytes. 4-Nitroquinoline 1-oxide (3 μM for 1 hr) was the most effective chemical examined for the production of chromosome abnormalities (approx 10% aberrations), but its effectiveness was limited by its cytotoxicity. ^{60}Co γ-rays, however, induced very prominent chromosome aberrations with a dose-effect relationship. WI-38 cells irradiated four times with 300-400 rads for a total dose of 1,400 rads showed neoplastic transformation starting about 150 days after the last irradiation. The transformed cells exhibited an epitheliallike morphology, abnormal karyology, and the B-type isoenzyme pattern of glucose-6-phosphate dehydrogenase, and they produced sarcomas when transplanted into the cheek pouches of hamsters treated with anti-hamster thymocyte serum. They have been cultured for 13 mo without showing aging phenomena. (25 refs)

78-5731 **Removal of Plutonium from Beagles Using Ca-DTPA and Zn-DTPA: Effects of Initial DTPA Injection.** (Eng) Taylor, G. N. (Radiobiology Lab., Univ. Utah, Salt Lake City, UT, 84112); Lloyd, R. D.; E man, J. J.; Atherton, D. R.; Mays, C. W. *Health Phys* 3 201-210; 1978.

The use of trisodium calcium diethylenetriaminepentaac (Ca-DTPA) and zinc diethylenetriaminepentaac (Zn-DTPA) for prompt treatment of radioactive pluto (^{239}Pu) exposure was compared in the dog. Sixteen be about 23 mo of age were each injected with 1 μCi ^{239}Pu 0.2 μCi ^{237}Pu as Pu(IV) citrate and then divided into groups of two males and two females each. About 1/ later, Group A dogs were injected iv with 30 μm Ca-DTPA/kg, Group B and C dogs with 300 μ Zn-DTPA/kg, and dogs in Group D dogs with 34 μ Zn-DTPA/kg. Subsequent treatments for Groups A, C, D were single daily sc injections of 34 μmole/kg Zn-DT Group B received 6.8 μmole Zn-DTPA/kg 5 x/day (dose, 34 μmole/kg/day). Pu retention in liver and non tissue was determined 3, 7, and 14 days after radionu injection. Retention in livers and kidneys was also meas after the dogs were killed at 14 days. There were no sig cant differences in total-body retention at 2 wk for Gr A, B, and C (190, 230, and 26%, respectively); in eac these groups retention was significantly lower than in G D (48%). Liver ^{239}Pu content was significantly lowe Groups A, B, and C (5.50, 4.30, and 4.4%, respectively in Group D (14.4%) or controls (35%) at 14 days. Kid content did not differ among the groups. Prompt treatm with 300 μmole Zn-DTPA/kg or 30 μmole Ca-DTPA provided superior clearance of radioactive Pu. It did not ter whether the subsequent daily treatment with 34 μ Zn-DTPA/kg was given in a single injection or in five i tions. (40 refs)

78-5732 **Early Retention of ^{237}Pu and ^{239}Pu in Ma Beagles.** (Eng) Lloyd, R. D. (Radiobio Lab., Univ. Utah, Salt Lake City, UT, 84112); McFarl S.; Atherton, D. R.; Bruenger, F. W.; Taylor, G. N.; M C. W. *Health Phys* 35(2): 211-215; 1978.

Early retention, excretion, and tissue distribution ^{239}Pu(IV)citrate (0.05-01 μCi/kg iv), to which tracer amo of the photon-emitter ^{237} Pu had been added, were studie five beagle dogs, age 57-84 mo. Pu retention in liver an nonliver tissue, mainly skeletal, was measured periodicall living dogs for nearly 4 mo. The mature beagles reta about 30% Pu in the liver and 50% in the skeleton a 10-120 days after injection (3 mo-old beagles have been fo to retain 12% in the liver and 68% in the skeleton). relative distribution of skeletal Pu among various bone the mature animals was similar to that seen previously i to 23 mo-old dogs, but different from that of 3 mo-old gles. An exception was the humerus for which there wa significant difference ($p > 0.2$) in the percentage of reta skeletal Pu for juvenile, young adult, and mature dogs. A 14%-20% of the injected Pu was excreted in urine and f in the first 3 wk after injection. Less uniformity in excre

retention was observed in mature animals than has been rted for younger dogs. (15 refs)

5733 **Decorporation from Beagles of a Mixture of Monomeric and Particulate Plutonium using DTPA and Zn-DTPA: Dependence upon Frequency of inistration.** (Eng) Lloyd, R. D. (Radiobiology Lab., . Utah, Salt Lake City, UT, 84112); Boseman, J. J.; Tay- G. N.; Bruenger, F. W.; Atherton, D. R.; Stevens, W.; s, C. W. *Health Phys* 35(2): 217-227; 1978.

use of Zn-diethylenetriaminepentaacetate (DTPA) and DTPA in the removal of radioactive plutonium was stud- in 14 young adult beagles (av age, 19.8 mo). The dogs e injected with 0.9 μCi/kg polymeric ^{239}Pu to which tracer unts of gamma-ray emitting ^{237}Pu had been added. Two later, four dogs were injected with 30 μmoles/kg DTPA /day and four dogs, with 30 μmoles/kg Ca-DTPA e per wk. Total ^{237}Pu excretion in the first 24 hr averaged % after Ca-DTPA, 10.4% after Zn-DTPA, and 7.1% in trols. Corresponding levels after 28 days, corrected for oactive decay, were 38.2%, 49.4%, and 12.1%, respec- ly. In the untreated dogs, there was a gradual transloca- of ^{237}Pu from the liver to nonliver tissue (mainly skeletal) r a 6-23 wk period. Biological retention of ^{237}Pu in nonliver ue remained constant for 6 wk in Ca-DTPA treated bea- , but the radionuclide in the liver decreased from 60% 4%. In Zn-DTPA treated animals, activity from liver and liver tissue declined from 60% to 25% and 28% to 17%, ectively, over 6-wk period. It is concluded that daily in- ions of Zn-DTPA are more effective in the removal of orporated plutonium than are weekly injections of DTPA. (38 refs)

5734 **Plutonium Retention, Excretion, and Distribution in Juvenile Beagles Soon after Injection.** g) Lloyd, R. D. (Radiobiology Lab., Univ. Utah, Salt e City, UT, 84112); McFarland, S. S.; Atherton, D. R.; ys, C. W. *Radiat Res* 75(3): 633-641; 1978.

order to determine the possible effects of environmental tonium on humans, ^{239}Pu was injected iv into six 3-mo-old gles. Dogs were injected with 0.4 μCi ^{239}Pu as the citrate nplex and 0.4 μCi ^{237}Pu to faciliate measurement of the All excreta were collected for the first 3 wk after injec- n, and Pu content determined by NaI spectrometry. About % of the injected Pu was excreted in the first 21 days, 5% urine and 6% in feces. Retention in liver and in nonliver ue (mainly skeleton) was measured serially in living dogs a combination of total- and partial- body counting, utiliz- the 60- and 100 kiloelectron volt photons from ^{237}Pu. The gs were sacrificed at 7, 14, 28, 56, 89, and 119 days after ection, respectively. Total excretion for living dogs for the ire 21-days collection period was roughly 11%, with about in urine and 6% in feces. Early retention of Pu in liver was lower in these dogs (11%-15%) than that observed previously in adults aged 17 mo (31%-37%), but early skeletal retention was greater for juveniles (62%-75%) than for adult (50%-60%). Pu content of most other tissues was similar in adults and juveniles. Compared with adults, juveniles had a significantly greater fraction (2- to 5-fold) of skeletal Pu in the paws and lower leg bones and a significantly lower fraction (2-fold) in the rib cage and thoracic and lumbar vertebrae. (12 refs)

78-5735 **Trophic Transfer by Chironomids and Distribution of Plutonium-239 in Simple Aquatic Microcosms.** (Eng) Trabalka, J. R. (Environmental Sciences Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830); Frank, M. L. *Health Phys* 35(3): 492-494; 1978.

The transfer of plutonium (Pu) from labeled organic sediments to chironomids, the most important component in the diet of juveniles and adults of many freshwater fish, was determined. Adult *Chironomus riparius* from a laboratory culture were stocked in aerated aquatic microcosms that had been spiked with plutonium-239 nitrate. Three microcosms were spiked twice, at the start and on day 69, with 0.01, 0.10, and 1.0 μCi/cm^3, respectively. Patterns of Pu concentration with time were similar at all concentrations following both additions. The distribution coefficient (ratio of Pu in sediments to that in water) at equilibrium was 7.88, 1.22, and 1.78 x 10^4 in the microcosms that received spikes of 0.01, 0.1 and 1.0 μCi/cm^3, respectively. Eleven *Chironomus* larvae were collected on day 73, and trophic transfer factors (TTF) for Pu to *Chironomus* from labeled sediments were calculated. The TTF values were similar to those for other invertebrates and fish taken from a more complex system contaminated with ^{237}Pu. The actual amount of Pu absorbed from food by *Chironomus* apparently was 0.1%-1% of that in the diet. The results indicate that organic sediments are not a sink for Pu but rather a pool with a significant, though small, available fraction for transfer to the next trophic level. (11 refs)

See also:
*(Rev.): 78-5434, 78-5444, 78-5445, 78-5446, 78-5447, 78-5451.
*(Chem.): 78-5477, 78-5513, 78-5521, 78-5633, 78-5651, 78-5661, 78-5665, 78-5671, 78-5678, 78-5685.
*(Viral): 78-5769, 78-5810, 78-5853.
*(Immun.): 78-5858, 78-5860.
*(Path.): 78-5872, 78-5873, 78-5897, 78-5898.
*(Epid.-Biom.): 78-5922, 78-5926, 78-5959, 78-5970, 78-5972, 78-5973, 78-5975, 78-5976.

78-5736 **Identification of an Avian Oncovirus Polyprotein in Uninfected Chick Cells.** (Eng) Eisenman, R. (Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104); Shaikh, R.; Mason, W. S. *Cell* 14(1): 89-104; 1978.

Studies of the nature of the *gag* gene product synthesized in uninfected chicken embryo fibroblasts (CEF) positive for the expression of avian oncovirus group-specific antigen (gs+) are reported. This product was shown to be a polypeptide with a mol wt of 120,000 daltons (P120). Its presence could not be correlated with the phenotypic expression of endogenous oncovirus envelope glycoprotein. Immunoprecipitation experiments indicated that it contains antigenic determinants of the virion core proteins (products of the *gag* gene) and reverse transcriptase, but not of the envelope glycoprotein gp85. Chromatography of the tryptic digests indicated that P120 contains amino acid sequences related to the virion core proteins $p27_o$, p19, and p12 of Rous-associated virus type 0 (RAV-0), but that it lacks the tryptic peptides of p15. Further studies were consistent with the idea that P120 is equivalent to a *gag-pol* polyprotein that is missing both p15 and significant portions of reverse transcriptase. In pulse-chase experiments, P120 did not appear to be specifically cleaved to generate virion structural proteins. Furthermore, P120 was not detected in RAV-0-producing line 7 and line 15 CEF. Instead, only Pr76-gag (the direct precursor to virion core proteins in productively infected cells) was observed. Thus, P120 is unlikely to act as a functional intermediate in virus maturation. Infection of gs+ CEF with exogenous avian sarcoma and leukemia viruses resulted in a significant but variable decrease in the level of P120. (71 refs)

78-5737 **Protein Kinase Activity Associated with the Avian Sarcoma Virus *src* Gene Product.** (Eng) Collett, M. S. (Dept. Pathology, Univ. Colorado Medical Center, Denver, CO, 80262); Erikson, R. L. *Proc Natl Acad Sci USA* 75(4); 2021-2024; 1978.

Evidence is presented for the association of protein kinase activity with the avian sarcoma virus (ASV) *src* gene product (p60-*src*). Incorporation of phosphorus from (γ-^{32}P)ATP into protein was catalyzed by specific immunoprecipitates from ASV-transformed avian and mammalian cells. This incorporation was observed only when antiserum from tumor-bearing rabbits able to precipitate p60-*src* specifically was used to immunoprecipitate antigens from transformed cell lysates. Immunoprecipitates of extracts from normal cells or cells infected with a transformation-defective ASV mutant showed no activity in this assay, nor did any immune complexes formed with normal rabbit serum or any of the cell extracts tested. The expression of protein kinase activity (ATP:protein phosphotransferase) was growth temperature-dependen cells infected with an ASV mutant temperature-sensitive transformation. It is speculated that protein phosphoryla may be involved in viral transformation by impeding nor assembly of cellular components. (21 refs)

78-5738 **Purification of Virus-specific RNA from Ch en Cells Infected with Avian Sarcoma Vi Identification of Genome-Length and Subgenome-Length ral RNAs.** (Eng) Parsons, J. T. (Dept. Microbiology, U Virginia Sch. Medicine, Charlottesville, VA, 22901); Le P.; Dierks, P. *J Virol* 27(1): 227-238; 1978.

Avian sarcoma virus (ASV)-specific RNA was purified f ASV-infected chick embryo (CE) cells by hybridizing p deoxycytidylic acid-elongated complementary DNA to A RNA and then chromatographing the annealing mixture polyinosinic acid-Sephadex columns. The purity and nuc tide sequence of the purified virus-specific RNA were es lished by rehybridization experiments and analysis of lab RNase T_1-resistant oligonucleotides by two-dimensi polyacrylamide gel electrophoresis. Cultured CE cells v infected with Prague ASV, subgroup B or C (PrC); with l tislava ASV, subgroup C; or with transformation-defec (td) PrC (a virus with a deletion of the sarcoma gene). lyadenylic acid-containing RNA purified from ASV-infe cells contained approx 1%-4% virus-specific RNA, c pared with 0.06%-0.15% in uninfected cells. Sucrose gr ent analysis of the virus-specific RNA isolated from infe cells revealed two major classes of polyadenylated viral R with sedimentation values of 36S and 26S-28S. Cells infe with td PrC contained 34S and 20S-22S viral RNA spe Double-label experiments employing infected cells lab initially for 48 hr with ^{3}H-uridine and then for 30, 60, or min with ^{32}P-phosphate showed that the intracellular cumulation of genome-length RNA (36S) was significa faster than that of the subgenomic 26S-28S viral RNA cies. The possible functions of the different species are cussed. (33 refs)

78-5739 **Peptide Analysis of the Transformation-spe Antigen from Avian Sarcoma Virus-tr formed Cells.** (Eng) Brugge, J. (Dept. Pathology, U Colorado Medical Center, Denver, CO, 80262); Erikson Collett, M. S.; Erikson, R. L. *J Virol* 26(3): 773-782; 1

Virus-specific proteins from chicken, hamster (2 lines), field vole cells transformed by the Schmidt-Ruppin strai avian sarcoma virus (SR-ASV) were isolated by immu precipitation and subjected to peptide analysis. Sera from

r-bearing rabbits (TBR) precipitated two proteins with
l wts of 76,000 daltons (76K) and 60K from all
V-transformed cell lines. One-dimensional peptide anal-
s of the 60K proteins indicated that the proteins from all
r transformed cell lines were identical. Two-dimensional
ptide analysis of the Pr76 and 60K proteins indicated that
60K protein was not related to Pr76 and that the observed
nigration of the four tryptic peptides of Pr76 and 60K was
tuitous. When cell extracts from ASV-transformed chick
ls radiolabeled with ^{32}P were immunoprecipitated with
R serum, a phosphorylated protein believed to be identical
60K was immunoprecipitated. Precipitation of this protein
s not blocked when TBR serum was first adsorbed with
rupted virions, although precipitation of the ^{32}P-labeled
ecursor to group-specific antigens, Pr76, was blocked un-
r these conditions. The tryptic phosphopeptides of 60K
otein from transformed chicken and field vole cell lines
grated identically during two-dimensional peptide anal-
is, and their migration differed from that of the principal
osphopeptide of Pr76. The acid hydrolysates of Pr76 and
K contained phosphoserine, and 60K contained a small
nount of phosphothreonine. The data show that the 60K
otein is transformation-specific, virus-coded, and unrelated
the structural proteins of ASV. (25 refs)

8-5740 Identification of Tumor-Specific Cell Surface Antigens from Quail Fibroblasts Transformed Avian Retro-Viruses and Chemical Carcinogens. (Eng) ubsamen, H. (Institut fur Virologie der Justus-Liebig-Uni-ersitat Giessen, Bereich Humanmedizin Frankfurter Strasse 07, 63 Giessen, W. Germany); Ignjatovic, J.; Hayami, M.; auer, H. *In: Advances in Comparative Leukemia Research 977. Proceedings of the VIIIth International Symposium on Comparative Research on Leukemia and Related Diseases, eld in Amsterdam, The Netherlands on 22-26 August, 1977.* entvelzen, P.; Hilgers, J.; Yohn, D. S., eds. (New York: lsevier/North Holland Biomedical Press): 503 pp.; 351-352; 977.

our tumor-specific antigens were detected on the surface of uail fibroblasts transformed by avian sarcoma virus or by ethylcholanthrene (MC) in an in vitro cellular mi-rocytotoxicity (CMC) assay: s-gp85, the viral envelope lycoprotein; g-gp85, an additional antigenic site of gp85 ex-osed only on tumor cells; a tumor-specific antigen of irus-transformed cells; and an embryonic antigen expressed n both MC- and virus-transformed cells. Soluble extracts of hese cells blocked the CMC reaction. (3 refs)

8-5741 Biochemical Properties of p15-associated Protease in an Avian RNA Tumor Virus. (Eng) Dittmar, K. J. (Max-Planck-Institut fur Molekulare Genetik, 000 Berlin 33, W. Germany); Moelling, K. *J Virol* 28(1): 06-118; 1978.

The biochemical properties of a proteolytic activity associated with avian myeloblastosis virus structural protein p15 were studied. Ion-exchange column chromatography and size fractionation analysis confirmed that all protease activity resided in the p15 fragment. The purity of p15 was assured by an isoelectric focusing procedure in polyacrylamide gels. Upon serological analysis with monospecific antibodies, p15 reacted with anti-p15 serum only and not with anti-p12 or anti-p27 sera. The proteolytic activity of p15 was demonstrated with bovine serum albumin (BSA), concanavalin A, casein, and ovalbumin. These substrates were denatured before p15 treatment by heat and sodium dodecyl sulfate. The optimum pH for this activity was 5.7. The effects of p15 were similar to those of papain, but papain had a much stronger proteolytic activity and it could not be applied over the same concentration range (0.1-2 μg) as p15. The parallel behavior of p15 papain was further demonstrated by their responses to proteolytic inhibitors. When p15 was incubated with polyprotein precursors precipitated from lysed Rous-associated-virus (RAV-6)-infected chicken cells, precursor Pr76 was cleaved. If anti-p15 serum was added, cleavage of Pr76 was inhibited. This indicates that p15 has a direct action on Pr76. (45 refs)

78-5742 **Virus-coded Origin of a 32,000-Dalton Protein from Avian Retrovirus Cores: Structural Relatedness of p32 and the β Polypeptide of the Avian Retrovirus DNA Polymerase.** (Eng) Schiff, R. D. (St. Louis Univ. Medical Center, Inst. Molecular Virology, St. Louis, MO, 63110); Grandgenett, D. P. *J Virol* 28(1): 279-291; 1978.

A 32,000-dalton polypeptide (p32) located in avian retrovirus cores was characterized by radioimmunoprecipitation (RIP) and biochemical techniques and was hypothesized to be related to the β polypeptide of the $\alpha\beta$ form of avian myeloblastosis virus (AMV) DNA polymerase, ^{35}S-methionine-labeled AMV virions were radioimmunoprecipitated (RIPD) with sarc III antiserum derived from Syrian hamsters bearing avian sarcoma virus-induced tumors. Precipitation of the DNA polymerase and p32 indicated that they were encoded by the viral genome. ^{125}I-labeled AMV p32 purified directly from plasma AMV was also RIPD by sarc III antiserum. AMV p32 was RIPD by goat and rabbit anti-AMV $\alpha\beta$ DNA polymerase; polypeptides α and β were RIPD by rabbit anti-AMV p32 protein, but polypeptide β was precipitated to a much greater extent. Therefore, AMV p32 and the β polypeptide of AMV DNA polymerase shared common antigenic determinants. Peptide mapping with sodium dodecyl sulfate-polyacrylamide gel electrophoresis after partial chymotryptic or *Staphylococcus aureus* V-8 protease digestion showed that all peptides demonstrable from AMV p32 were also present in the digests of the β polypeptide. Conversely, no common sequences were found between p32 and the α polypeptide. These results indicate that p32 is derived from the β polypeptide of AMV $\alpha\beta$ DNA polymerase by proteolytic cleavage, but that it is structurally unrelated to the α polypeptide. (46 refs)

78-5743 **Discrimination of DNA Polymerase and RNase H Activities in Reverse Transcriptase of Avian Myeloblastosis Virus.** (Eng) Gorecki, M. (Dept. Organic Chemistry, Weizmann Inst. Science, Rehovot, Israel); Panet, A. *Biochemistry* 17(12): 2438-2442; 1978.

The functional amino acid residues in the active sites of avian myeloblastosis virus (AMV) reverse transcriptase were examined. Viral DNA polymerase activity was 3.6-fold more sensitive to the sulfhydryl- and amino-group-specific reagent N-ethylmaleimide (NEM) than was RNase H activity. Incubation of the enzyme in the presence of polynucleotides resulted in partial protection of both activities against NEM, whereas nucleotide triphosphate did not affect the inactivation rate. The interaction of NEM with DNA polymerase was temperature-dependent. NEM inactivated DNA polymerase with Pka's of 5.5 and 6.5 and RNase H with a pKa of 7.5. The hydrophobic agents 5,5′-dithiobis(2-nitrobenzoic acid) (DTNB), p-hydroxymercuribenzoic acid, and 2-nitro-5-thiocyanobenzoate (NTCB) were potent inhibitors of DNA polymerase activity, but they did not affect RNase H. Hydrophilic agents such as iodoacetic acid, iodoacetamide, and ethylenimine had no effect on AMV reverse transcriptase. Since pretreatment of DNA polymerase with DTNB did not prevent NEM from reacting with a residue necessary for the activity of this enzyme, two different reactive groups are probably involved with this activity. RNase H was completely inactivated by short preincubation at pH <4.5, but it was only 50% inactivated at pH 5.0. DNA polymerase was unaffected at pH 4.3-8.3, and sharp inactivation was observed only below pH 4.3. The inactivation caused by preincubation at low pH was irreversible and was not time-dependent. The data indicate that the DNA polymerase and RNase H activities reside on independent active sites that may partially overlap but can be distinguished by suitable chemical modifications. (22 refs)

78-5744 **A Virus-induced Non-virion Antigen Specific for Transformation at the Surface of RSV-transformed Fibroblasts.** (Eng) Comoglio, P. M. (Dept. Human Anatomy, Univ. Torino Medical Sch., 10126 Torino, Italy); Prat, M.; Bertini, M. *Nature* 273(5661): 381-383; 1978.

Studies were made of the antigenic composition of BHK-C13/21 hamster fibroblasts transformed in vitro by Rous sarcoma virus (RSV) mutants either defective for the synthesis of envelope glycoproteins or temperature-sensitive for the ability to transform the host cell. These cells were found to express a tumor-specific antigen with the following properties: it is expressed at the surface of hamster cells transformed by RSV but not by unrelated RNA or DNA oncogenic viruses, it is expressed by RSV-transformed cells of different animal species, and it is not one of the known structural virion proteins. It was named the virus cell-surface antigen (VCSA). Experiments with the temperature-sensitive mutant indicated a strict correlation between the appearance of VCSA at the cell surface and expression of the transforming *sarc* gene. VCSA may be the product of the *sarc* gene may be coded by a cellular gene under control of this g (26 refs)

78-5745 ***Ts pol* Mutants of Avian Sarcoma Viruses: M ping and Demonstration of Single Cycle Rec binants.** (Eng) Alevy, M. C. (Dept. Microbiology, U Southern California Sch. Medicine, 2025 Zonal Ave., Angeles, CA, 90033); Vogt, P. K. *Virology* 87(1): 21-33; 1

Twenty-seven early coordinate temperature-sensitive (ts) tants of the Prague strain of Rous sarcoma virus were is ed, and the position of the mutants in the *pol* gene was d mined by three-factor crosses using the known polyme mutant *LA337* and the *env* marker. The effect of tempera shifts on the transforming abilities of the mutants indic that each mutant contains an early coordinate lesion could interfere with the initiation but not maintenanc transformation. All mutants behaved in a qualitatively s lar manner except *LA354*, which appeared to be a mul mutant containing both late transformation and early coo nate lesions. Temperature shifts had similar effects on replicative abilities of all mutants. The data indicated tha early coordinate lesion acted at 42 C to abort the infect cycle before a stable association between virus and host c be formed. The polymerase activity of each mutant was n thermolabile then that of wild-type virus in vitro. Three tor crosses between *LA337* B and the new mutants *L* to *LA377* suggested that wild-type progeny clones obta from the crosses were true recombinants and that recomb tion between the *ts* markers occurred at low frequency. relative proportions of each class of progeny remained f constant between 48 and 96 hr after the infected cells mixed, the wild-type recombinants having been formed b hr after mixing. All of the new mutants mapped betv *LA337* and the *env* gene. The data suggest that the 7 isolates were all polymerase mutants and that heterozyg are not obligatory precursors of recombinants. (39 refs)

78-5746 **Disk Gel Electrophoresis and Infrared S troscopy of the Proteins in Rous Sarcoma sue.** (Rus) Klenina, N. V. (Ukrainian Res. Inst. Experime Veterinary Medicine, Kharkov, USSR); Antonov, V Chorna, L. D. *Ukr Biokhim Zh* 50(4): 520-525; 19

Disk gel electrophoresis and infrared spectroscopy were to analyze the proteins in Rous sarcoma tis Thirty-day-old Leghorn chickens were inoculated im Rous sarcoma virus homogenate (0.2 ml); tumor specir were analyzed on days 3, 6, 10, and 15 postinoculation. electrophoretogram of normal thoracic muscle consiste 18 protein fractions. Tumor development resulted in ma changes in all these fractions, especially in fast-protein c the albumin level increased from 1.32% to 15% on day and the prealbumin level increased from 1.68% to 3.

mpared with control thoracic muscle specimens, Rous sarna tissue lacked two absorption bands at 1,100 and 800 $^{-1}$. (12 refs)

-5747 **Characterization of the *env* Gene in Avian Oncoviruses by Heteroduplex Mapping.** (Eng) Hu, S. (Dept. Microbiology, Univ. Southern California Sch. edicine, Los Angeles, CA, 90033); Lai, M. M.; Vogt, P. K. *Virol* 27(3): 667-676; 1978.

ne *env*-specific nonhomology between ring-necked pheasant rus (RPV) and chicken leukosis and sarcoma viruses was ed as the basis for a study of the *env* gene by heteroduplex apping using electron microscopy. The *env*-specific region nonhomology was 1.5-1/7 kilobases (kb) long. Its 3′ undary was at 0.6-0.7 kb from the 3′ end of the genome transformation-defective (*td*) viruses and at about 2.5 kb nondefective avian sarcoma viruses. This estimate is simir to that obtained by oligonucleotide fingerprinting. Comarison of several strains of avian oncoviruses showed that ne 3′ half of this *env* region is conserved and the 5′ half is ore divergent. A small area at the very 3′ end of the *env* so showed divergence between the different avian oncovirus airs tested. The data argue against the possibility of an unecognized gene between *env* and *src*. In heteroduplex molecules between *td* and nondefective sarcoma virus genomes, ne *src* deletions and the *env* nonhomology region are contiguus, and their size is equal to the sum of the *src* and *env* genes. Iowever, the possible presence of a very short region of spacr sequences between *env* and *src* could not be ruled out. Comparison of the glycoproteins from various avian onoviruses by gel electrophoresis showed that those of RPV gp60, gp33) and Chinese quail virus (gp55, gp29) differed n mol wt from the glycoproteins of the chicken oncoviruses gp85, gp37). (32 refs)

78-5748 **Lack of Serologic Identity of Marek's Disease Associated Tumor Surface Antigen (MATSA) n Various Marek's Disease Cell Lines.** (Eng) Sharma, J. M. (Regional Poultry Res. Lab., ARS, U.S.D.A., 3606 E. Mt. Hope Road, East Lansing, MI, 48823); Nazerian, K.; Stephens, E. A.; Witter, R. L. *In: Advances in Comparative Leukemia Research 1977. Proceedings of the VIIIth International Symposium on Comparative Research on Leukemia and Related Diseases, held in Amsterdam, The Netherlands on 22-26 August, 1977.* Bentvelzen, P.; Hilgers, J.; Yohn, D. S., eds. (New York: Elsevier/North Holland Biomedical Press): 503 pp.; 191-192; 1978.

Serologic relationships between Marek's disease (MD) tumor-associated surface antigen (MATSA) on MD cell lines (MSB-1, RPL-1, and HPRS-1) and an MD-derived transplant (MDT) were studied by complement-independent antibody cytotoxicity assay. There was a one-way reaction between MSB-1 and RPL-1 cells: RPL-1 antiserum reacted with MSB-1 cells, but MSB-1 antiserum did not cross-react with RPL-1 cells. Because of possible contamination of MSB-1 and RPL-1 sera with antibody to histocompatibility antigens, the reactivity of these sera could not be related directly to MATSA. However, the results with MDT antiserum, which lacked histocompatibility antibody, clearly indicated that MDT shared a common surface antigen with MSB-1 and HPRS-1 but not with RPL-1. The RPL-1 antiserum cross-reacted with MDT and HPRS-1 as well as with MSB-1. (5 refs)

78-5749 **Demonstration of Cells with Marek's Disease Tumor-associated Surface Antigen (MATSA) in Peripheral Blood of Chickens with Marek's Disease Lymphoma.** (Eng) Sato, T. (Hokuwa Livestock Hygiene Service Center, Nara, Japan); Wataki, K.; Matsuda, H.; Kato, S. *Biken J* 21(1): 33-35; 1978.

The existence of Marek's disease (MD) tumor-associated surface antigen (MATSA)-positive cells in the peripheral blood of chickens with MD lymphoma is reported. Eight of 10 chickens given 10^7 MD tumor cells (line MSB-1) ip developed typical MD lymphoma between 46 and 140 days of age. MATSA-positive cells were found in the peripheral blood of four of these eight chickens and in one of the two chickens without lymphoma, but not in the peripheral blood of controls. In the chickens with lymphomas, the percentages of MATSA-positive cells among peripheral WBC ranged from 0.2% to 1.5%. Autopsy studies of commercial chickens suspected of having MD or lymphoid leukosis (LL) revealed 26 cases of MD and 5 of LL. MATSA-positive cells were found in the peripheral blood of 22/26 MD chickens but in none of the LL chickens The percentage of positive cells in the peripheral blood of the 22 chickens ranged from 0.3% to 5%. No MATSA-positive cells were found in the peripheral blood of healthy chickens. The correlation between MD lymphoma incidence and MATSA-positive cells in the peripheral blood suggests that the latter may be useful in diagnosing MD. (9 refs)

78-5750 **Interaction of Marek's Disease and Rous Sarcoma Viruses During Mixed Infection in Chickens.** (Rus) Sedunov, Z. A. (All-Union Res. Veterinary Inst. Poultry Farming, Moscow, USSR); Korovin, R. N.; Neidbailik, I. E. *Veterinariia* (7): 43-46; 1978.

Characteristic features of the interaction of Marek's disease virus (MDV) and Rous sarcoma viruses (RSV) during mixed infection were analyzed by inoculating white Leghorn chickens with RSV (0.1 ml, im) and/or MDV (0.2 ml, ip). All chickens inoculated with RSV alone died within 19 days; 36.6% of the chickens inoculated with MDV died within 60 days (necropsy showed lymphoid infiltrates in 46.6% of these birds). Simultaneous injection of RSV + MDV induced both tumors (60%) and lymphomas (43.3%). The duration of sur-

vival of chickens inoculated with RSV + MDV was 11-26 days longer than that of chickens inoculated with RSV alone. (no refs)

78-5751 **Identification of the *Mtv*-2 Gene Responsible for the Early Appearance of Mammary Tumors in the GR Mouse by Nucleic Acid Hybridization.** (Eng) Michalides, R. (Div. Genetics, Antoni van Leeuwenhoekhuis, Netherlands Cancer Inst., Amsterdam, Netherlands); van Deemter, L.; Nusse, R.; van Nie, R. *Proc Natl Acad Sci USA* 75(5): 2368-2372; 1978.

The number of mammary tumor virus (MTV) proviral sequences associated with the Mtv-2 gene was investigated by nucleic acid hybridization between MTV ^{3}H-complementary DNA (cDNA) and DNA from GR, C57BL/10JA (B10), and GR-*Mtv*-2- mice. Both B10 and GR-*Mtv*-2- mice lack *Mtv*-2 gene expression. The DNA of GR mice contained 12 copies of MTV proviral sequences, whereas only four copies were present in the DNA of B10 and GR-*Mtv*-2- mice, leading to the conclusion that the *Mtv*-2 gene in the GR mouse strain is associated with eight additional *MTV* proviral sequences. These results indicate that the GR genome contains two sets of MTV sequences. One is associated with the *Mtv*-2 gene and controls the early appearance of mammary tumors in the GR mouse, and the other is responsible for MTV RNA expression in GR-*Mtv*-2 mice. Different amounts of MTV RNA were detected at first lactation in the mammary gland of B10 and GR-*Mtv*-2 mice, even though both contain four copies of MTV proviral sequences. This indicates a difference between the two strains either in the regulation of expression of these MTV proviral sequences or in their location in the murine genome. (19 refs)

78-5752 **Cultivation of Mouse Mammary Tumor Cells Derived from DD/Tr.** (Eng) Iwai, Y. (No affiliation given); Iwai, M.; Takamori, Y.; Okumoto, M. *Annual Report Radiation Center Osaka Prefecture* 18: 113-117; 1978.

The relationship between changes in cell-surface structure and the production of murine mammary tumor virus (MuMTV) by a cell line derived from a spontaneous mammary tumor in a female DD/Tbr mouse was studied in the presence and absence of insulin (INS) or dexamethasone (DXM). Most of the cells cultured with INS or DXM were epithelioid, but fibroblastic cells always appeared in the domes. RNA-dependent DNA polymerase (RDDP) activity was detected in the culture fluid of cells grown in the presence of the hormones, but not in the culture fluid of cells grown in their absence. This activity began to increase about 11 days after seeding; it reached a max level after 14-17 days and then declined. Murine leukemia virus was not detected in the cells by XC-plaque tests or by a focus-forming assay using mink S + L- cells. Scanning electron microscopy of the mammary tumor cell surfaces in the early cultures revealed many short microvilli and viruslike particles that increased with th crease in RDDP activity. Thus, there is a close relatio between the appearance of short microvilli and viruslike ticles on the cell surface and the release of virus int culture medium. (5 refs)

78-5753 **Changes in MuMTV DNA and RNA Leve Balb/c Mammary Epithelial Cells Du Malignant Transformation by Exogenous MuMTV an Hormones.** (Eng) McGrath, C. M. (Dept. Biology, Mich Cancer Foundation, Detroit, MI, 48201); Marineau, Voyles, B. A. *Virology* 87(2): 339-353; 1978.

Concentrations of murine mammary tumor virus (MuM sequences in the DNA and RNA of normal BALB/c m mary epithelial cells were compared with concentratio virus- and hormone-induced premalignant and malig derivatives to determine if changes in steady-state Mu RNA levels occur during malignant transformation. No mammary cells contained multiple (5 or 6) copies of Mu sequences in DNA. Malignant mammary cells, transfo after MuMTV infection, contained two to three times number of MuMTV sequence copies. These extra Mu sequences were not detected in the DNA of normal m mary epithelial cells of MuMTV-infected females o MuMTV-induced premalignant cells. Neither malignant premalignant mammary cells transformed after prolo exposure to mammotropic hormones contained in the a tional MuMTV sequences. MuMTV sequences detecte malignant BALB/c mammary epithelial cells, regardles transforming agent, were indistinguishable by DNA-com mentary DNA (DNA-cDNA) hybrid thermal denatura from the MuMTV sequences in the DNA of normal c Mammary adenocarcinomas induced by MuMTV o mammotropic hormones contained 30- to 50-fold higher centrations of MuMTV RNA than normal mammary of young animals. Similarly high concentrations were de ed in premalignant cells. It is concluded that change steady-state MuMTV RNA concentrations take place du premalignant and malignant stages of transformation. refs)

78-5754 **Mammary Tumor Virus Oncogenesis and mor Immunogenicity in Three Sublines of C3H Mouse.** (Eng) Vaage, J. (Dept. Cancer Therapy De opment, Pondville Hosp., Walpole, MA, 02081); Medina *Cancer Res* 38(8): 2443-2447; 1978.

Mammary tumorigenesis and mammary tumor transpla tion immunogenicity were compared in three C3H mo sublines: standard mammary tumor virus (MTV-S)-infe C3H/He mice; MTV-S-infected C3H/Ki mice; MTV-S-free C3H/He mice. The age at appearance of the tumor, the growth rate of the tumors in their first transp generation, and the immunogenicity of each tumor in s

c female recipients were determined for the first tumor ppear in each of 25 breeding females from each of the sublines. The early appearance of the tumors was relat- the presence of the MTV-S. The genetically dissimilar nes C3H/He and C3H/Ki, both infected with MTV-S, loped mammary tumors at an av age of 10 mo, 11 mo re MTV-S-free C3H/He mice. The tumor characteristics mmunogenicity and growth stimulation were related to genetic factors. The genetically similar sublines C3H/He C3Hf/He developed similar proportions of immunogenic growth stimulating mammary tumors; the genetically rgent C3H/Ki subline developed tumors that were mmunogenic and that tended to be strongly growth ulating. (20 refs)

5755 **Observations on the Question of Horizontal Transmission of Mouse Mammary Tumor s.** (Eng) Moore, D. H. (Dept. Microbiology and Im- ology, Hahnemann Medical Coll. and Hosp., Phila- hia, PA, 19102); Holben, J. A. *Cancer Res* 38(8): 5-2457; 1978.

igen and tumor incidences in weanling BALB/c and BL mice living for 5 wk in cages with murine mammary or virus (MuMTV)-infected females were compared with trol BALB/c and C57BL mice living in the same labora- . All mice were bred continuously, and third-lactation s were tested for MuMTV antigen by the Ouchterlony roimmunodiffusion test. Although the antigen incidence significantly greater, mammary tumor incidence in the emates was not significantly different from that in con- ls. Mice inoculated with phosphate-buffered salt solution 02 M phosphate, PH7.4; 0.15 M NaCl; and 0.1% bovine um albumin) and sham-inoculated mice also had an elevat- antigen incidence. Repeat tests of milks at the fourth or h lactations indicated that > 50% of those positive at the rd became negative at later lactations. Factors that may ve stimulated MuMTV antigen secretion are discussed. (20 s)

-5756 **In Vivo Activities of B-tropic Isolates from Mice of Strain C57BL/Ka.** (Eng) Decleve, A. ancer Biology Res. Lab., Dept. Radiology, Stanford Univ. edical Center, Stanford, CA, 94305); Lieberman, M.; Trav- M.; Kaplan, H. S. *In: Advances in Comparative Leukemia search 1977. Proceedings of the VIIIth International Sym- sium on Comparative Research on Leukemia and Related seases, held in Amsterdam, The Netherlands on 22-26 Au- st, 1977.* Bentvelzen, P.; Hilgers, J.; Yohn, D. S., eds. (New rk: Elsevier/North Holland Biomedical Press): 503 pp.; 0-162; 1978.

e detection of virus-specific cytoplasmic antigens by in- ect immunofluorescence was used to follow virus replica- n in the lymphoid and hematopoietic tissues of C57BL/Ka mice inoculated with three B-tropic viruses isolated from that strain: radiation leukemia virus (RadLV), BL/Ka(6), and BL/Ka(B). Virus doses were 6 x 10^4 particles/inoculum in newborns and 5 x 10^5 particles/inoculum in animals aged 1 wk or older. The BL/Ka(B) and BL/Ka(6) isolates were essentially nonthymotropic after iv or ip inoculation. After direct intrathymic inoculation, BL/Ka(6) was able to infect and transform the thymic lymphocytes, but BL/Ka(B) lacked this ability. However, BL/Ka(B) could productively infect hematopoietic or lymphoid tissues when injected in neonates, which suggests that nonleukemogenic viruses may contribute to leukemogenesis in C57BL/Ka mice. The thymotropic and leukemogenic activity of BL/Ka(6) was 10^5 times lower than that of RadLV. (7 refs)

78-5757 **Presence of Oncornavirus-like Particles in the P388 Murine Leukemic Cell Line.** (Eng) Schmidt, J. M. (Dept. Botany and Microbiology, Arizona State Univ., Tempe, AZ, 85281); Pettit, G. R. *Experientia* 34(5): 659-660; 1978.

P388 murine lymphoblastoid cells were examined for the presence of virus like particles. Almost every sectioned cell observed had C-type oncornavirus like particles budding at the plasma membrane or, occasionally, into an intracytoplasmic vesicle. Intracytoplasmic A-type and immature B-type particles were also observed. The discovery of oncornavirus like particles in the P388 cell line increases the utility of this neoplastic system for detecting potential antineoplastic agents. (3 refs)

78-5758 **Endogenous RNA Tumor Viruses Are Activated During Chemical Induction of Murine Plasmacytomas.** (Eng) Armstrong, M. Y. (Dept. Epidemiology and Public Health, Yale Univ. Sch. Medicine, 333 Cedar St., New Haven, CT, 06510); Ebenstein, P.; Konigsberg, W. H.; Richards, F. F. *Proc Natl Acad Sci USA* 75(9): 4549-4552; 1978.

A study was made of the endogenous expression of murine leukemia virus (MuLV) in BALB/cAn female mice inoculated with the potent plasmacytoma-inducing oil pristane (2,6,10,14-tetramethylpentadecane: 0.5 ml ip) at age 6, 14, and 23 wk. Spleen, mesenteric lymph node, thoracic lymph node, and peritoneal exudate cells were prepared from treated and control mice over a 10-mo period, and the cell suspensions were assayed for infectious MuLV's. Tumors appeared in the treated mice after age 32 wk. From 28 to 50 wk, the percentage of ecotropic virus-positive mice and the number of virus-positive cell samples rose sharply in the treated mice (24/36 mice, 54/105 samples) compared with controls (4/22 mice, 11/58 samples). The percentage of xenotropic virus-positive samples was also consistently higher in treated mice, and virus was isolated from these mice throughout the observation period. Xenotropic MuLV could not be detected

in any control samples obtained at 28, 32, and 39 wk. Both ecotropic and xenotropic endogenous MuLV were expressed in those sites where foci of transformed plasma cells subsequently appear; ie, peritoneal exudate cells and thoracic lymph node cells. The significance of the preferential expression of ecotropic and xenotropic MuLV in target cell populations following administration of a carcinogen is discussed in terms of the possible formation of an oncogenic variant virus. (37 refs)

78-5759 **Serological Characterization of B-tropic Viruses of C57BL Mice. Possible Origin by Recombination of Endogenous N-tropic and Xenotropic Viruses.** (Eng) Benade, L. E. (Cancer Biology Program, NCI Frederick Cancer Res. Center, Frederick, MD, 21501); Ihle, J. N.; Decleve, A. *Proc Natl Acad Sci USA* 75(9): 4553-4557; 1978.

The serological characteristics of two independent sets of N- and B-tropic viruses isolated from C57BL/6 mice and C57BL/Ka mice were examined. Radioimmune competition assays for various virion components revealed that the N-tropic and B-tropic viruses were readily distinguishable by assays for the viral proteins p15 and p12, whereas these viruses were serologically identical by competition assays for proteins gp71 and p30. In addition, the N-tropic viruses had p12's serologically identical to that of AKR murine leukemia virus (MuLV), but the B-tropic viruses had p12's serologically identical to that of B-tropic radiation leukemia virus VL-3. The C57BL/6 N-tropic virus had a p15 identical to AKR MuLV p15, whereas the C57BL/Ka N- and B-tropic viruses and the C57BL/6 B-tropic virus had a serologically distinct p15. The results suggest that the endogenous N-tropic virus of C57BL mice undergoes recombination with the endogenous xenotropic virus and that this mechanism is involved in the generation of B-tropic viruses in these mice. (30 refs)

78-5760 **Abrogation of Fv-1b Restriction with Murine Leukemia Viruses Inactivated by Heat or by Gamma Irradiation.** (Eng) Bassin, R. H. (Lab. Tumor Virus Genetics, NCI, Bethesda, MD, 20014); Duran-Troise, G.; Gerwin, B. I.; Rein, A. *J Virol* 26(2): 306-315; 1978.

The mechanism by which Fv-1b restriction in BALB/3T3 cells is abrogated following infection with N-tropic murine leukemia virus was investigated by comparing the inactivation rates for viral infectivity and for the ability of the same virus to abrogate Fv-1 restriction. Inactivation of the abrogating ability of N-tropic murine leukemia virus following graduated doses of gamma radiation (0-2.5 x 10^6 rads) proceeded at half the rate of that for viral infectivity. This indicated that viral RNA must function in abrogating Fv-1b restriction but that only a portion of the viral genome is required. The inactivation kinetics of N-tropic murine leukemia virus were determined following incubation of virus at 43 C. Abrogat ability of N-tropic murine leukemia virus was found to about six times as stable under these conditions as was v infectivity. Virion-associated reverse transcriptase acti was inactivated at the same rate as was viral infectivity, dicating that this enzyme may not be needed during abro tion. When virus was heated to 43 C, abrogation was t sient, requiring 6-9 hr after virus infection to beco maximally effective and then beginning to disappear after prox 18 hr. These findings confirm the idea that abrogat of Fv-1 restriction can be separated experimentally from vi replication. (33 refs)

78-5761 **Differences in the Properties of Cytoplas Particles and in the Expression of Virus-spec Information in the Thymus of Normal and Lymphomat AKR Mice.** (Eng) Gurgo, C. (Inst. Molecular Virology, Louis Univ. Medical Center, St. Louis, MO, 63110); Bonc ant, M. C.; Bridges, S. H. *Cancer Res* 38(8): 2473-2479; 19

The properties of viruslike cytoplasmic particles in thy tissue from normal and lymphomatous AKR mice and expression of leukemia-related sequences in these tissues w investigated. The retrovirus nature of the particles was dicated by the presence of RNA-dependent DNA polymer (reverse-transcriptase) and by the chromatographic prop ties of the purified enzyme. Equilibrium centrifugation s dies revealed a difference in the buoyant densities of the pa cles extracted from the two types of tissue. A density of 1. g/ml was estimated for particles of lymphomatous thy tissue and for the Gross passage A virus, a leukemoge AKR murine leukemia virus MuLV, compared with 1. g/ml for thymic particles from normal (1- and 2-mo-o mice. Molecular hybridization studies aimed at detecting ferences in the expression of viral-specific information RNA from the normal and lymphomatous thymic tiss were carried out with a Moloney MuLV complement DNA (cDNA) probe. From 40% to 50% of the probe hyb dized with the RNA from normal thymic tissue with equivalent value of the product of the time (sec) of hybridi tion and the RNA concentration (moles of nucleotides/lit at which 50% hybridization was reached being indicative approx 100 genome equivalents of endogenous viral RNA cell. About 80% of the probe hybridized with the RNA fr lymphomatous tissue. Viral-related RNA in the lymphom tous tissue consisted of two abundance classes: one cl (homologous with 50% of the probe) was hybridized at a r suggestive of about 2,400 viral genome equivalents/c Thus, in the lymphomatous thymus, virus-specific RN expression was not only increased quantitatively (relative normal thymus) it was characterized by the expression qualitatively 'new' sequences. The melting temperature of h brids of MuLV cDNA with RNA from normal and ly phomatous tissue was 83 C. A melting temperature of 91 was observed for hybrids composed of the probe and homo gous Moloney MuLV 70S RNA. (32 refs)

5762 **Structural Analysis of the Surface Glycoproteins (GP70's) of Recombinant Murine ype Viruses: Evidence for Envelope Gene Recombina-** (Eng) Elder, J. H. (Scripps Clinic and Res. Foundation, 6 N. Torrey Pines Road, La Jolla, CA); Jensen, F. C.; tsch, J. W.; Lerner, R. A.; Vogt, M. *In: Advances in parative Leukemia Research 1977. Proceedings of the th International Symposium on Comparative Research on kemia and Related Diseases, held in Amsterdam, The herlands on 22-26 August, 1977.* Bentvelzen, P.; Hilgers, ohn, D. S., eds. (New York: Elsevier/North Holland nedical Press): 503 pp.; 156-159; 1978.

surface glycoprotein gp70 from parental and recombit murine C-type viruses was analyzed by tryptic peptide erprinting. The recombinant viruses tested included R-247, HIX, MoMCF22, and the radiation-induced leuia virus 136.5. The results showed that the recombinants e the products of recombination between ecotropic and otropic C-type viruses and that recombination took place hin the envelope gene encoding gp70. (12 refs)

5763 **Scanning Electron Microscopy of Lymphoid Cells from Leukemia Virus-infected Mice.** g) Farber, P. A. (Dept. Pathology, Temple Univ. Sch. ntistry, Philadelphia, PA, 19122); Specter, S.; Friedman, *Infect Immun* 20(3): 816-826; 1978.

een, lymph node, bone marrow, and thymus cells from end leukemia virus (FLV)-infected inbred male BALB/c ce were examined at various times after infection by scang electron microscopy. The presence of cells with surface munoglobulin (SIg) molecules, theta antigen, and leunia virus-associated or -induced surface antigens was demined by immunofluorescence. Within 3-5 days after intion, the number and percentage of spleen cells with villous ojections decreased and, concomitantly, the number of cells at were larger and smoother increased. Within 10-20 days er infection, the majority of splenocytes were smooth, large ls showing many distinct morphological changes, includg surface holes and a spongy appearance. By 25 to 35 days er infection, most splenocytes were abnormal in appearce. Similar changes occurred in the lymph nodes, but at slower rate. Thymus and bone marrow cells showed little ange in surface morphology until late in infection, and even en only a few cells appeared abnormal. Changes in the leen cells but not the lymph node cells paralleled a rapid crease in the percentage of cells that were positive for SIg d theta antigen. FLV antigen appeared rapidly on spleen lls after infection; fewer lymph node cells were positive and ly low numbers of marrow and thymus cells. The morphogical changes detected among the lymphoid cell populaons appear to correlate directly with the immunosuppreson induced by the virus. These results, therefore, suggest at there is a direct relationship between infection and alterion of lymphoid cell type and morphology. (26 refs)

78-5764 **Requirement of Protein Synthesis for the Degradation of Host mRNA in Friend Erythroleukemia Cells Infected with Herpes Simplex Virus Type 1.** (Eng) Nishioka, Y. (Dept. Microbiology, Coll. Physicians and Surgeons, Columbia Univ., New York, NY, 10032); Silverstein, S. *J Virol* 27(3): 619-627; 1978.

Friend erythroleukemia (FL) cells were used to elucidate the viral mechanisms responsible for inhibition of the synthesis of host-specific proteins in cells infected with herpes simplex virus. Shortly after infection, cellular polyribosomes (PR) dissociated and cellular messenger RNA (mRNA) degraded. Analysis of infected cell extracts on sucrose density gradients demonstrated that most of the PR had dissociated to monoribosomes at 2 hr postinfection. Physical measurements of infected cells RNA's supported this conclusion and also showed that the polyadenylated RNA's had decreased in size. The degradation of mRNA was apparently stochastic, as the relative abundance of adenylated globin mRNA remained constant at 2 and 4 hr postinfection. However, it is possible that different cellular mRNA's may be degraded at different rates. In experiments on the effects of pactamycin and sodium fluoride on PR and globin mRNA, it was found that dissociation of PR was not sufficient to account for the rapid degradation of globin mRNA, as the amount of globin mRNA in uninfected cells did not change when cells were treated with these substances at concentrations sufficient to dissociate all PR. In cells infected with UV-irradiated virus, PR dissociated but globin mRNA did not degrade, which suggests that it is possible to separate the two events. It is concluded that the dissociation of PR appears to be mediated by a heat-labile, virion-associated function and that degradation of the mRNA requires expression of the virus genome. This conclusion is substantiated by additional experiments with superinfected FL cells, irradiated virus, and cycloheximide. (37 refs)

78-5765 **A Neutralization Bioassay for Friend Leukemia Virus.** (Spa) Basombrio, M. A. (Seccion Leucemia Experimental, Instituto de Investigaciones Hematologicas, Academia Nacional de Medicina, Buenos Aires, Argentina); Genovese, J. *Medicina (B Aires)* 38: 245-249; 1978.

A method for the titration of Friend Leukemia Virus (FLV) in mice was standardized. The method is based on the direct relationship, at high virus doses, between the virus dose injected and spleen wt 14 days later. If, before inoculation, the virus is incubated with specific antiserum for 1 hr at 37 C, neutralization occurs, and the prevention of splenomegaly is proportional to the concentration of virus-specific antibodies in the serum. Regressing sarcomas induced in mice by a sarcoma virus pseudotype of FLV induced resistance to challenge with FLV. Sera from these animals strongly neutralized the virus. Mice in which leukemia was induced by FLV also had virus-neutralizing antibodies, but to a lesser extent than the immunized mice. A preliminary search was carried out for antibodies to FLV in 20 normal human sera and in 29

sera from patients with leukemia. Although the serum from some subjects neutralized the virus, no significant differences were detected between the normal and leukemic samples. (11 refs)

78-5766 **Intracellular Restriction of Ecotropic Murine Leukemia Virus in Rat NRK Cells and Its Abolishment by Adaptation.** (Eng) Yoshikura, H. (Dept. Genetics, Inst. Medical Science, Univ. Tokyo, Tokyo, Japan); Yoshida, M. *J Virol* 27(3): 612-618; 1978.

Ecotropic murine leukemia viruses (MuLV-E) are partially restricted in normal rat kidney (NRK) cells. This is true for both the N-tropic FN-2 (purified helper component of Friend leukemia virus) and the B-tropic WNB-2 (purified WN1802B BALB/c-derived endogenous virus) viruses. Successive passages of the viruses in NRK cells resulted in a stable adaptation that was manifested in increased plaquing efficiency and the formation of clear and large plaques in NRK cells. The NRK cells were more susceptible to FN-2 virus than to WNB-2 virus, and the adaptation was more complete in the former. The adaptation seemed to occur mainly at the level of intracellular growth of MuLV-E in NRK cells, and no changes in the mobilities of the viral proteins gp69/71 and p30 in sodium dodecyl sulfate-polyacrylamide gel electrophoresis were observed after the adaptation of FN-2 in NRK cells. It appeared that the restriction of MuLV-E in NRK cells was not due to penetration but mainly to intracellular growth, although the former may not be excluded completely. Since both FN-2 and WNB-2 were subjected to two successive limiting dilutions in mouse SC-1 cells and were obtained from cells infected with the virus diluted 2 logarithmic units higher than the limit of plaque formation in NRK cells, the adaptation was not due to a simple selection of NRK-nonrestricted virus that had existed before NRK passage. The adaptation seemed to be initially induced by a host modification, followed by selection. Possible commitment of xenotropic virus in the adaptation was excluded. The host-induced changes in FN-2 and WNB-2 were stable even if the adapted viruses were propagated back into SC-1 cells. The adaptation was host-specific; ie, MuLV-E adapted in NRK cells failed to replicate efficiently in other rat cell lines of different origins. This suggests that host cell-specific RNA or DNA sequences are involved in the adaptation. (22 refs)

78-5767 **Generation of Oncogenic Type C Viruses: Rapidly Leukemogenic Viruses Derived from C3H Mouse Cells In Vivo and In Vitro.** (Eng) Rapp, U. R. (Lab. Viral Carcinogenesis, NCI, NIH, Bethesda, MD, 20014); Todaro, G. J. *Proc Natl Acad Sci USA* 75(5): 2468-2472; 1978.

The generation of oncogenic C-type variants from a poorly infectious virus isolated from C3H/10T1/2 mouse cells (low-leukemia strain) is reported. The parent virus did not cause tumors upon inoculation into newborn NIH mice, but variants with increased infectivity for mouse were derived both in vivo and in vitro by selecting for va able to grow to high titers. The highly infectious va were able to induce mouse fibroblasts to grow in soft Inoculation of the viruses into newborn NIH Swiss mi sulted in 100% mortality from leukemia within 4 mo; tumors developed at the injection site. Both mouse-tropi dual-tropic viruses were isolated from the leukemic mic plaque-purified. The first group of viruses produced syncytial plaques on rat XC cells and did not grow in cells. The viruses of the other group replicated well in mouse and mink cells, producing morphologic changes lar to transformation but not XC syncytia. This indi that they are members of the MCF class of murine C viruses. Isolates from either group were highly leukemo on retesting: the mean latent period was 67 days mouse-tropic virus and 105 days for a dual-tropic vir was concluded that there is a positive correlation betwee ability of a mouse C-type virus to grow in cell culture its leukemogenic potential. Furthermore, it is possible to with a weakly infectious, nonleukemogenic virus and to vert it to a rapidly replicating, highly leukemogenic vir passage either in cell culture or in the animal. (16 refs

78-5768 **The Friend Spleen Focus-forming Virus (SF Genome: Fractionation and Analysis of S and Helper Virus-related Sequences.** (Eng) Mak, T. W. tario Cancer Inst., Univ. Toronto, Toronto, Ontario, C da); Penrose, D.; Gamble, C.; Bernstein, A. *Virology* 8 73-80; 1978.

High titers of Friend spleen focus-forming virus (SFFV) its helper lymphoid leukemia virus (LLV) propagate NIH/3T3 fibroblast cell cultures were analyzed by D fractionation and molecular hybridization to determine composition of the SFFV genome. When DNA complem tary to helper LLV RNA (cDNA-LLV) was hybridize viral RNA from stocks containing SFFV in apparent ex and to helper LLV RNA, the results indicated that there two populations of helper LLV sequences present in the R extracted from the Friend virus complex. cDNA complem tary to sequences unique to the SFFV genome was fractio ed by hydroxyapatite chromatography and was shown t homologous to sequences found only on the SFFV, and the LLV, genome. Three cDNA probes were used to de virus-specific sequences in SFFV nonproducer mouse and cell clones: cDNA-LLV, SFFV, cDNA-LLV, cDNA-SFFV. The results with the first probe suggested the RNA of cells producing SFFV contained sequences found in cells producing LLV. The results with the sec probe demonstrated that the two SFFV nonproducer clo expressed helper LLV sequences, but they suggested that SFFV genome contained only a portion of the sequen found on the LLV genome. cDNA-SFFV hybridized onl RNA from cells productively or nonproductively infec with SFFV. The data suggest that the SFFV genome conta

n SFFV-specific sequences and a portion, but not all, of helper LLV sequences. (24 refs)

-5769 **Antigenic Modulation of Leukemic Cells Induced by X-irradiation of the Host.** (Eng) Ioam, H. L. (Dept. Pathology, Lenox Hill Hosp., New York,); Pearse, A.; Sabbath, M. *In: Advances in Comparative ukemia Research 1977. Proceedings of the VIIIth Internaal Symposium on Comparative Research on Leukemia and lated Diseases, held in Amsterdam, The Netherlands on 26 August, 1977.* Bentvelzen, P.; Hilgers, J.; Yohn, D. S., . (New York: Elsevier/North Holland Biomedical Press): pp.; 349-350; 1977.

tigenic modulation was induced in vitro by adding the sera x-irradiated rats to an established tissue culture line of kemic cells that replicates Gross leukemia virus and is igenically positive. Indirect immunofluorescence and imnoelectron microscope techniques showed that murine kemia virus antigens formed patches and caps and gradu decreased in staining intensity. Virus particles were local d to only a few areas of the cell membrane. These changes re reversible. (9 refs)

-5770 **Viral Gene Expression in Murine Sarcoma Virus (Murine Leukemia Virus)-infected Cells.** ng) Dina, D. (Dept. Genetics, Albert Einstein Coll. Medie, New York, NY, 10461); Penhoet, E. E. *J Virol* 27(3): 8-775; 1978.

vels of viral gene expression were analyzed in Moloney rine sarcoma virus (murine leukemia virus) 124 ISV(MLV) 124]-infected NIH 3T3 cells, and the results re compared with those in MSV- and MLV-infected and infected cells. The MSV(MLV) complex was prepared m the supernatant of infected clone 124 TB cells. The SV(MLV)-infected cells produced virions that contained out 99% MSV RNA and 1% MLV RNA. Differences beeen these concentrations were also present in the nucleus, toplasm, and polysomes. However, MLV RNA was exessed at much higher levels in cells infected by MLV alone. ne most likely explanation for this situation is that, as a nsequence of MSV(MLV) infection, MSV proviral DNA present in excess, forcing MLV into secondary integration es that are transcribed at a much lower level. In SV(MLV)-infected cells, three to four copies of proviral NA from each virus were integrated into the cellular DNA. easurements of RNA specific for each of the genomes by ybridization to specific complementary DNA reagents realed a 10- to 15-fold difference in concentration in both uclear and polysomal RNA fractions, with MSV RNA redominating in both cases. The results support the idea that ne production of MSV and MLV RNA's is regulated at the vel of transcription, and they show that the basic differences n concentration found in the viral particles originate at least artially in the cell nucleus. (38 refs)

78-5771 **Characterization of Viral-Type Nucleotide Sequences Detected in the RNA of Human Leukemia Cells by Probes of Murine and Simian Origin.** (Fre) Tavitian, A. (Laboratoire d'Hematologie experimentale, Hopital Saint-Louis, 2, place du Dr. Fournier, F75475 Paris Cedex, France); Hamelin, R.; Larsen, C. J.; Marty, M.; Peries, J.; Boiron, M. *Bull Cancer (Paris)* 65(1): 25-30; 1978.

Molecular hybridization techniques were used to detect viral genomes in the RNA of cells from patients with acute myelocytic leukemia (AML), acute lymphocytic leukemia (ALL), and chronic myelocytic leukemia (CML) and in the RNA of normal WBC. Complementary DNA (cDNA) prepared from Moloney murine sarcoma-leukemia virus [M-MSV(MLV)] and from simian sarcoma virus and its associated virus [SSV-(SSAV)] was used as the molecular probe. Hybridization was slight or absent in cells from the blood and spleen of the four normal subjects. In cells from the 15 leukemia patients, hybridization ranged from 0% to 13.5% for the SSV-(SSAV) probe and from 0% to 43% for the M-MSV(MLV) probe. The probes did not react exclusively with any one type of leukemia cell. Nucleotide sequences common to both probes, isolated and used as a single probe, failed to detect viral RNA in leukemia cells that had hybridized with the complete cDNA from either M-MSV(MLV) or SSV-(SSAV). A recycled probe used in cells from three AML patients succeeded in hybridizing; therefore, the complementary nucleotide sequences are probably distributed along the viral genome. (10 refs)

78-5772 **5′-Terminal Nucleotide Sequences of Mammalian Type C Helper Viruses Are Conserved in the Genomes of Replication-defective Mammalian Transforming Viruses.** (Eng) Tronick, S. R. (Lab. RNA Tumor Viruses, NCI, Bethesda, MD, 20014); Cabradilla, C. D.; Aaronson, S. A.; Haseltine, W. A. *J Virol* 26(3): 570-576; 1978.

The RNA's of replication-defective murine and primate C-type transforming viruses were analyzed for nucleotide sequences homologous to the genomes of their helper viruses using complementary DNA (cDNA) probes generated from the total or 5′-terminal regions of Moloney murine leukemia virus and woolly monkey virus RNA. The defective viruses had been shown previously to vary in their ability to express helper *gag* gene proteins. With total RNA cDNA probes, the transforming viruses varied greatly in their representation of helper virus sequences (15%-60% hybridization). In contrast, the 5′-terminal-specific sequences of the helper virus were conserved in the RNA's of every transforming virus tested (> 80% hybridization). These findings suggest a critical role of these sequences in the life cycle of the defective transforming viruses. (41 refs)

78-5773 **A Comparative Study of Two Rat Viral Complexes: MSV(RaVL) and KiMSV(RHHV).**

(Eng) Yang, S. S. (NCI, Bethesda, MD, 20014); Ting, R. C. *In: Advances in Comparative Leukemia Research 1977. Proceedings of the VIIIth International Symposium on Comparative Research on Leukemia and Related Diseases, held in Amsterdam, The Netherlands on 22-26 August, 1977.* Bentvelzen, P.; Hilgers, J.; Yohn, D. S., eds. (New York: Elsevier/North Holland Biomedical Press): 503 pp.; 264-266; 1978.

A Moloney sarcoma MSB-1 virus rat leukemia virus pseudotype and a Kirsten sarcoma virus rat hepatoma helper virus pseudotype were found to have a common sedimentation value of 1.145-1.155 g/cm^3. They also demonstrated common antigenic determinants, using antisera specific against rat leukemia virus; no reactivity was demonstrated against mouse C-type virus antisera. Proteins of mol wt 110,000 (110K)-120K, 70K, 30K, and 7K-10K daltons were present in variant amounts; the nature of these proteins is outlined. (4 refs)

78-5774 **Moloney Leukemia Virus-determined Cell Membrane Antigens.** (Eng) Fenyo, E. M. (Dept. Tumor Biology, Karolinska Inst., 104 01 Stockholm 60, Sweden); Troy, F. A.; Siegert, W.; Klein, E. *In: Advances in Comparative Leukemia Research 1977. Proceedings of the VIIIth International Symposium on Comparative Research on Leukemia and Related Diseases, held in Amsterdam, The Netherlands on 22-26 August, 1977.* Bentvelzen, P.; Hilgers, J.; Yohn, D. S., eds. (New York: Elsevier/North Holland Biomedical Press): 503 pp.; 331-336; 1978.

A cell surface antigen (MCSA) that is present in Moloney leukemia virus-induced lymphomas was separated from viral proteins and histocompatibility antigens (H-2) by a sequence of purification procedures. Sodium dodecyl sulfate-gel electrophoresis revealed two subunits with a mol wt of 92,000 and 50,000 daltons, respectively. A Moloney lymphoma cell line characterized by low MCSA expression produced a variant virus deficient in MCSA-inducing activity. This suggests that MCSA is virally determined. (14 refs)

78-5775 **Production of 'Rapid-Harvest' Moloney Murine Leukemia Virus by Continuous Cell Culture on Synthetic Capillaries.** (Eng) Ratner, P. L. (Dept. Biochemistry, Univ. Kentucky Medical Center, Lexington, KY, 40506); Cleary, M. L.; James, E. *J Virol* 26(2): 536-539; 1978.

The use of synthetic capillaries for the continuous large-scale recovery of Moloney murine leukemia virus (M-MuLV) from chronically infected NIH/3T3 cells is reported. With this method, the M-MuLV could be automatically harvested within 60 min of release from the cells in quantities of approx 100 ml/24 hr/capillary unit. Virus production and infectivity were measured by determination of reverse transcriptase activity and by the XC syncytia assay. The optimum period for harvesting the virus was from days 4 to 11 inclusive. A max infectious titer of virus (> 10^9 plaque-forming units/ml) noted by day 8. These results indicate that the use of synt capillary units for the production of rapid-harvest RN mor virus is an alternative to the roller bottle and cu flask methods. (24 refs)

78-5776 **Relationship of Retrovirus Polyprotein C ages to Virion Maturation Studied with Ten ature-sensitive Murine Leukemia Virus Mutants.** (Witte, O. N. (Dept. Biology, Massachusetts Inst. Tech gy, Cambridge, MA, 02139); Baltimore, D. *J Virol* 2 750-761; 1978.

The processing of murine leukemia virus (MuLV) proteins in cells infected by the temperature-sensitive (*ts*) tants Moloney *ts*3 and Rauscher *ts* was studied. Both *ts*3 *ts*24-infected cells grown at the restrictive temperature (accumulated large numbers of late-budding structures small numbers of early-budding forms. Cells infected wild-type Moloney MuLV or *ts*3 or *ts*24 at the permi temperature (32.5 C) contained budding structures a stages of development. At the restrictive temperature, *ts* mutants accumulated the core precursor polypro Pr65(gag) and Pr180(gag-pol); little Pr80(env) or Pr90 was cleaved, but a large fraction was degraded. After a to the permissive temperature, Pr65(gag) and Pr180(gag were cleaved and released into virions. The final prod p30 and p85, built up with time in the virions, and p30 not p85, was maintained at a steady-state level in the infe cells. Uncleaved Pr65, Pr180, and Pr130 were all reduce incubation at the permissive temperature in serum-free m um, and the appearance of finished reverse transcriptase evident. Reduction of the *gag* intermediates and an inc in p30 also occurred. Reverse transcriptase as an activ zyme appeared only when Pr180(gag-pol) had been cle to form the active p85 protein. This cleavage occurred m ly, if not entirely, after the release of virions from the (39 refs)

78-5777 **Identification of Virus Found in Mouse l phomas Induced by HIX Murine Oncornav** (Eng) Fischinger, P. J. (Lab. Viral Carcinogenesis, NCI thesda, MD, 20014); Dunlop, N. M.; Blevins, C. S. *J* 26(2): 532-535; 1978.

Four lymphomas induced by pure HIX murine leuk virus, two each in BALB-2 and NIH Swiss mice, were fo to contain large amounts of virus with amphotropic pro ties. Analysis of tumor-derived virus purified by limiting tion techniques indicated that its interference and neutra tion spectra were essentially identical to parental HIX and different from ecotropic and xenotropic viruses. Ex nation of virus progeny from many individual foci ind by virus derived directly from lymphomas indicated that infectious unit contained only HIX virus. No evidence of tropic virus was observed. (13 refs)

778 **Structural Studies on Rauscher Murine Leukemia Virus: Isolation and Characterization of l Envelopes.** (Eng) Van de Ven, W. J. (Dept. Biochemis- Univ. Nijmegen, Geert Grooteplein Noord 21, Nijmegen, erlands); Vermorken, A. J.; Onnekink, C.; Bloemers, H. Bloemendal, H. *J Virol* 27(3): 595-603; 1978.

isolation and characterization of viral envelope struc- from disrupted virions of Rauscher murine leukemia are reported. The virions were isolated from tissue cul- medium of chronically infected NIH Swiss 3T3 mouse ryo cells. Disruption of the virions was achieved with um dodecyl sulfate or Nonidet P-40 in combination with r. Fractionation into a viral core fraction and a viral en- pe fraction was performed through flotation in a discon- ous sucrose gradient. The amount of the *gag* and *env* -encoded structural polypeptides in the virions and the ted envelope fraction was compared using sensitive com- ion radioimmunoassays or sodium dodecyl te-polyacrylamide gel electrophoresis after immuno- ipitation with polyvalent and monospecific antisera di- ed against Rauscher murine leukemia virus proteins. The lominant viral structural polypeptides in the purified en- pe fraction were the *env* gene-encoded polypeptides gp70, (E), and p12(E). Only relatively small amounts of the *gag* e-encoded structural polypeptides p30, p12, and p10 were sent in the envelope fraction; however, a relatively high ount of the *gag* gene production p15 was detected in this tion. (30 refs)

5779 **Immune Lysis of Type C Viruses by Antisera to Purified Viral Subunits.** (Eng) Oroszlan, S. ral Oncology Program, Frederick Cancer Res. Center, . Box B, Frederick, MD, 21501); Gilden, R. V. *In: Ad- ces in Comparative Leukemia Research 1977. Proceedings the VIIIth International Symposium on Comparative Re- rch on Leukemia and Related Diseases, held in Amster- m, The Netherlands on 22-26 August, 1977.* Bentvelzen, P.; gers, J.; Yohn, D. S., eds. (New York: Elsevier/North lland Biomedical Press): 503 pp.; 90-93; 1978.

mune virolysis was used to study the localization of specif- virion polypeptides, evaluate the specificity of antisera, and ermine the presence of host cell antigens in the viral en- ope. Complement-dependent specific lysis of labeled uscher murine leukemia virus was obtained with anti-gp70 d anti-p15(E) sera, confirming the surface localization of se subunits. Lysis by antisera to normal cells and by specif- sera to serologically defined alloantigens demonstrated that st antigens are incorporated into the viral envelope. (12 fs)

-5780 **Impaired Gene Expression of Rauscher Murine Leukemia Virus.** (Eng) van de Ven, W. J. (Dept. ochemistry, Univ. Nijmegen, Geert Grooteplein Noord 21, Nijmegen, Netherlands); van Zaane, D.; Vermorken, A. J.; Bloemers, H. P. *In: Advances in Comparative Leukemia Research 1977. Proceedings of the VIIIth International Symposium on Comparative Research on Leukemia and Related Diseases, held in Amsterdam, The Netherlands on 22-26 August 1977.* Bentvelzen, P.; Hilgers, J.; Yohn, D. S., eds. (New York Elsevier/North Holland Biomedical Press): 503 pp.; 163-167; 1978.

The impaired expression of the genes coding for the structural polypeptides (*gag* and *env* gene products) of Rauscher murine leukemia virus (R-MuLV) was studied. In NIH/3T3 cells infected with temperature-sensitive R-MuLV mutants, impaired expression of the *gag* gene was observed at the restrictive temperature. *Gag*-pr65 accumulated, but *gag*-pr75 disappeared and p30 was not produced. Production of the *env*-related polypeptide p12(E) was also inhibited at the restrictive temperature. In R-MuLV-infected JLS-V9 cells, cytochalasin B (25 μg/ml) reversibly inhibited the synthesis of the glycosylated precursor peptide *env*-pr82 and the production of virus-specific gp69/71, p15(E), and p12(E). A similar but irreversible inhibition occurred in the presence of 2-deoxy-D-glucose (15 mM). (11 refs)

78-5781 **Origin of the Minor Glycoproteins of Murine Leukemia Viruses.** (Eng) Kemp, M. C. (Dept. Microbiology, Univ. Alabama in Birmingham, University Station, Birmingham, AL, 35294); Wise, K. S.; Edlund, L. E.; Acton, R. T.; Compans, R. W. *J Virol* 28(1): 84-94; 1978.

An attempt was made to prove that the minor virus-associated glycoproteins from Rauscher murine leukemia virus (R-MuLV) and from AKR thymic lymphoblastoid BW5147 cell membranes are proteolytic cleavage products of the major glycoprotein gp70. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) analysis of R-MuLV polypeptides grown in JLS-V9 cells and labeled with ^{3}H-glucosamine or ^{3}H-galactose + ^{14}C amino acids indicated the presence of two glycosylated polypeptides. The larger one weighed 72,000 (gp70), the smaller one 52,000 (gp52). Antiserum to gp70 precipitated both, indicating that they were antigenically related. When labeled R-MuLV virions were digested with increasing concentrations of trypsin and analyzed with SDS-PAGE, the amount of gp70 was reduced, with a corresponding direct increase in a smaller peptide weighing 52,000. The R-MuLV infectivity titer decreased by 69% upon digestion with 40 μg/ml trypsin. When gp70 and gp52 were digested with Pronase and treated with neuraminidase, gp70 was split into two polypeptides of mol wt 5,100 and 2,900. The 5,100-dalton fragment was the only significant entity resulting from gp52 digestion. Glycoproteins from detergent-extracted AKR thymic lymphoblastoid cell membranes were labeled with ^{125}I and subjected to radioimmunoprecipitation with various antisera. Goat anti-R-MuLV gp70 precipitated components of 40,000-50,000 mol wt and, to a lesser extent, a component of 30,000 mol wt. Tryptic digestion of iodinated glycoproteins from BW5147 cells produced

similar results. The appearance of similar glycoprotein components in AKR membrane preparations and R-MuLV preparations supports the contention that these minor glycoproteins arise from a cleavage of gp70. (39 refs)

78-5782 **Immune Response to Rauscher Virus-induced Leukemia in DBA Mice. II. Correlation Between Antigenic Expression and Pathogenesis.** (Eng) Toth, F. D. (Inst. Microbiology, Univ. Medical Sch., 4012 Debrecen, Hungary); Vaczi, L. *Neoplasma* 25(3): 265-272; 1978.

Immune responses to Rauscher virus-induced leukemia in DBA mice were studied to determine the mechanism leading to the lethal exacerbation of the disease. On the basis of changes in spleen wt, three stages of leukemia were distinguished: early progression, regression, and exacerbation. A significant tumor-specific (TS) antibody titer was first detected on the 12th after virus infection. This was followed by a fast rise to day 40, when the serum antibody level began to decline; no significant titer could be detected after day 60. During early progression (days 10-18) and regression (days 35-40), the sera of leukemic mice contained circulating immune complexes, with TS antibody in excess. This soluble antigen was identical to one of the two soluble TS antigens in the serum of Rauscher leukemic BALB/c mice. During exacerbation (days 50-65), soluble antigen was not found in the serum; thus, its accumulation in the circulation was not responsible for the lethal progression of the disease. Two types of disappearance of TS antigen were observed. Immediately before the beginning of regression, antigen could not be detected even after neuraminidase treatment. This and a rapid decrease in the number of tumor cells indicated that the antigenic receptor sites were lost as a consequence of the cytotoxic reaction mediated by TS antibodies. The presence of antigen-antibody complexes in the serum provided further evidence for this assumption. On the other hand, a new population of leukemic cells emerged during regression, and it appeared that these cells lost their specific surface antigenicity, probably because of masking of the receptor sites by sialic acid. The results illustrate that the simultaneous loss of immunosensitivity and immunogenicity of a virus-induced leukemia can occur spontaneously. The correlation between antigenic expression and pathogenesis raises questions about in vivo demasking of TS antigen receptors. (24 refs)

78-5783 **Retention of Transformant Specific Type III Collagen in Dibutyryl cAMP Treated Kirsten Sarcoma Virus Transformed BALB 3T3 Cells and in a Flat Revertant.** (Eng) Hata, R. (Dept. Tissue Physiology, Medical Res. Inst., Tokyo Medical and Dental Univ., Tokyo, Japan); Peterkofsky, B. *J Cell Physiol* 95(3): 343-352; 1978.

Kirsten sarcoma virus-transformed BALB 3T3 cells (Ki-3T3 cells) were treated with dibutyryl cyclic AMP (dbcAMP) to determine if the collagen phenotype could be restored to that of nontransformed cells. Ki-3T3 cells contained mainly t I collagen $[\alpha_1(I)]_2\alpha_2$, and approx 30% of a collagen desig ed type III $[\alpha_1(III)]_3$. BALB 3T3 cells contained mainly I collagen and about 25% of another type (X) compose three α_1 chains. Procollagen labeled with radioactive pr was isolated from the medium or cells of cultures and verted to collagen with pepsin. The collagen was analyze carboxymethylcellulose (CMC) chromatography or gel trophoresis under denaturing conditions. Ki-3T3 cells tre with 0.5 mM dbcAMP continued to accumulate type III lagen, but there was an increase in the number of α_1 ch eluting from CMC columns in the same position as c suggesting increased accumulation of type X collagen. though the revertant was similar to dbcAMP-treated cel that it exhibited a flattened morphology and a high rel rate of collagen synthesis, the collagen profile was simil that of the transformant, consisting mainly of types I and These findings indicate that accumulation of type III coll is unaffected by dbcAMP, but they suggest that cAMP be involved in the regulation of type X collagen. The fa of dbcAMP or reversion to affect the occurrence of typ collagen supports the mechanism of cell selection as a m of explaining the specific occurrence of type III collag Ki-3T3 cells. (18 refs)

78-5784 **Helper-independent Transformation by Un grated Harvey Sarcoma Virus DNA.** (Lowy, D. R. (Dermatology Branch, NCI, Bethesda, 20014); Rands, E.; Scolnick, E. M. *J Virol* 26(2): 291 1978.

A study was made of the unintegrated infectious DN Harvey sarcoma virus (Ha-SV) and Moloney leukemia (M-MuLV) obtained from the Hirt supernatant fracti cells acutely infected with these viruses. To obtain a q quantitative assay for infectious viral DNA, recipient m cells were first exposed to calcium phosphate-precipitate ral DNA and then treated with dimethyl sulfoxide. Infe ty was monitored by focus formation for Ha-SV and plaque formation for M-MuLV. The viral DNA titration tern followed single-hit kinetics for both foci and pla indicating that a single molecule carried information for function. Focus-forming and plaque-forming activities present in different molecules, since these two biologica tivities could be separated from each other by agaros electrophoresis. The focus-forming molecule was linear I with a mol wt of approx 4×10^6 daltons. The focus-for activity of the viral DNA was sensitive to *Eco*RI and resi to *Xho*I restriction endonucleases; plaque-forming ac was resistant to the former but sensitive to the latter. generation of helper-independent foci indicates that H DNA can transform mouse cells in the absence of helper or its proteins. (36 refs)

78-5785 **The Occurrence of Feline Leukaemia Neutralizing Antibodies in Cats.** (Eng) Ru

I. (ICRF Tumour Immunology Unit, Dept. Zoology, . Coll. London, London W.C.1E 6BT, England); Jarrett, *nt J Cancer* 22(3): 351-357; 1978.

occurrence of feline leukemia virus-neutralizing antibo- (ab's) to subgroups A (FeLV-A), B (FeLV-B), and C V-C) were determined in four cat populations: specif- thogen-free (SPF) cats, urban and suburban free-range) cats, cats from FeLV-infected multiple cat households H's), and leukemic cats. The prevalence of anti-FeLV-A was closely related to the frequency of isolation of V-A in each population, except in leukemic cats. Thus, vas found in 0% of SPF cats, 4% of FR cats, and 42% MCH cats. In individual MCH cats, there was a strong elation between the presence of ab's to FeLV-A and the nce of active FeLV viremia. Anti-FeLV-B ab's were en- ntered less frequently, although FeLV-B was present in rox half of the FeLV-B isolates. This was likely due to restricted growth of FeLV-B in cats. Surprisingly, in view the rare isolation of FeLV-C, the prevalence of -FeLV-C ab's was high: 11% in FR, 51% in MCH, and % in leukemic cats (none were found in SPF cats). Their urrence was not related to whether or not a cat was virem- Anti-FeLV-C ab's are likely evoked by an antigen that is ressed in cats during infection with FeLV-A: a possible didate is a determinant coded for by endogenous V-like genes present in cat cells. An interesting finding anti-FeLV-C ab's in cats with lymphosarcoma, especially eLV-negative cases, which implies that the cats had been osed at some time to FeLV-A. To determine how these ations might have arisen, cats from all the populations e experimentally infected by contact (C) or inoculation and examined for the presence of virus and neutralizing . The outcome of the infection was determined within 1 in I cats and 10 wk in C cats. In I cats, there was a marked ative correlation between the development of viremia and appearance of anti-FeLV-A ab's. However, the three emic cats, anti-FeLV-C ab's were found in the absence of s to FeLV-A. (21 refs)

5786 **Feline Oncornavirus Associated Cell Membrane Antigen: A Tumor Specific Cell Surface Mark-** (Eng) Essex, M. (Dept. Microbiology, Harvard Sch. Pub- Health, Boston, MA, 02115); Sliski, A. H.; Hardy, W. D.; Noronha, F.; Cotter, S. M. *In: Advances in Comparative ukemia Research 1977. Proceedings of the VIIIth Interna- nal Symposium on Comparative Research on Leukemia and lated Diseases, held in Amsterdam, The Netherlands on -26 August, 1977.* Bentvelzen, P.; Hilgers, J.; Yohn, D. S., . (New York: Elsevier/North Holland Biomedical Press): 3 pp.; 337-340; 1978.

ltured cells infected with feline leukemia virus (FeLV) or nsformed with feline sarcoma virus (FeSV) were examined the FeLV structural proteins p30 and gp70 and for feline cornavirus-associated cell membrane antigen (FOCMA). OCMA expression was found to be transformation-specific and independent of gp70 or p30 expression. Feline lymphoma and leukemia cells also expressed FOCMA, even in the absence of FeLV p30 and gp70. Lymphoid cells from normal cats, even those infected with FeLV, were negative for FOC- MA. (9 refs)

78-5787 **Presence of 5′-Terminal Cap Structures in Virus-specific RNA from Feline Leukemia Virus-infected Cells.** (Eng) Thomason, A. R. (Dept. Biology, Univ. California at Los Angeles, Los Angeles, CA, 90024); Friderici, K. H.; Velicer, L. F.; Rottman, F. *J Virol* 26(2): 226-235; 1978.

Experiments were conducted to determine whether intracellular Rickard strain Friend leukemia virus (R-FeLV)-specific RNA (vRNA) acting as messenger RNA (mRNA) is capped even though virion subunit RNA is not capped. F-422 feline thymus tumor cells, chronically infected with R-FeLV, were labeled with ^{32}P and the total cytoplasmic RNA was isolated. The RNA was centrifuged through sucrose gradients, and R-FeLV vRNA was located by hybridization of portions of the gradient fractions to R-FeLV complementary DNA. vRNA classes with av sedimentation coefficients of approx 36S, 28S, 23S, and 15S were identified. Each class of RNA was recovered and hybridized with mercurated R-FeLV complementary DNA, and the hybrids were chromatographed on columns of sulfhydryl-Sepharose to separate them from unhybridized cellular RNA. Although insufficient amounts of 36S and 28S vRNA were obtained for further analysis, the 23S and 15S vRNA classes were analyzed to determine the nature of their 5′ termini. Each of these vRNA classes contained stoichiometric amounts of cap structures per unit length of RNA, consistent with the presence of one cap per molecule. The structure of the 23S vRNA cap was $m^7G^{5'}ppp^{5'}GmpAp$, amd that of the 15S vRNA cap was $m^7G^{5'}ppp^{5'}GmpGp$. (34 refs)

78-5788 **Distribution of Bovine Leukemia Virus Proviral DNA Sequences in Tissues of Animals with Enzootic Bovine Leukosis.** (Eng) Kettmann, R. (Departement de Biologie Moleculaire, Universite Libre de Bruxelles, Brussels, Belgium); Burny, A.; Cleuter, Y.; Ghysdael, J.; Mammerickx, M. *Arch Int Physiol Biochim* 85(5): 989-991; 1977.

Bovine leukemia virus (BLV) single-stranded complementary DNA (cDNA; ^3H-thymidine-labeled DNA complementary to BLV 70S RNA) was used to study the distribution of proviral DNA sequences in tissues (normal or malignant) of bovine, ovine, porcine, and human origin. After recycling against normal bovine DNA, BLV ^3H-cDNA hybridized to bovine enzootic tumor DNA but failed to hybridize to normal bovine DNA, indicating that BLV is an exogenous RNA oncogenic virus and that enzootic bovine leukosis (EBL) is an infectious disease. Proviral BLV sequences were also detected in buffy-coat cells of animals with persistent lymphocytosis

and carrying antibodies to BLV but no tumors. In animals at the tumor stage of EBL, the proviral sequences were found in buffy-coat cells, in solid tumors (lymphosarcomas), and in organs infiltrated with tumoral lymphoid cells but not in apparently normal organs. No hybridization above background was observed between BLV ^{3}H-cDNA and DNA's extracted from buffy-coat cells and tumors corresponding to sporadic forms of bovine leukosis, porcine leukemia, and some leukemias and sarcomas. (3 refs)

78-5789 **Localization of Papillomavirus and Virus-specific Antigens in the Skin of Tumor-bearing *Mastomys natalensis* (GRA Giessen).** (Eng) Reinacher, M. (Veterinar-Pathologisches Institut, Justus-Liebig-Universitat Giessen, Frankfurter Strasse 96, D-6300 Giessen, W. Germany); Muller, H.; Thiel, W.; Rudolph, R. L. *Med Microbiol Immunol (Berl)* 165(2): 93-99; 1978.

Examination of the skin tumors of *Mastomys natalensis* (yellow, red-eyed Giessen) by electron microscope and immunofluorescence studies demonstrated *M. natalensis* papillomavirus particles and viral antigens in distinct epithelial layers in all tumors. Twenty-six spontaneous tumors (13 keratoacanthomas, 3 squamous cell carcinomas, 10 papillomas) and 24 experimentally induced tumors (20 keratoacanthomas, 4 squamous cell carcinomas) were collected from 33 male and 17 female mice. Upon EM investigation, virus particles were seen in the upper layers of the thickened stratum granulosum and in the stratum lucidum and the stratum corneum. In intact cells, virus particles were present exclusively in the nucleus; with increased keratinization, however, particles were distributed throughout the organelle-damaged cells. Particles were never seen in the stratum basale, stratum spinosum, or in the lower layers of the stratum granulosum. Antisera from tumor-bearing animals and laboratory rabbits produced identical fluorescence in each tumor type. The fluorescent areas corresponded to the location of the virus particles identified by the EM. All virus-specific material was restricted to the same distinct cell layers in all tumors, sites identical to those where papillomavirus-specific material has been demonstrated in papillomas of other species, including humans. (7 refs)

78-5790 **Virus-induced Papillomas of the Alimentary Tract of Cattle.** (Eng) Jarrett, W. F. (Dept. Veterinary Pathology, Univ. Glasgow Veterinary Sch., Bearsden, Glasgow, G61 1QH, Scotland); Murphy, J.; O'Neil, B. W.; Laird, H. M. *Int J Cancer* 22(3): 323-328; 1978.

The incidence of alimentary papillomas (AP) in 7,746 cattle of a wide age range from northern England and Scotland was determined in an abattoir survey. The overall incidence of AP was 19%, and the tumors were found at four sites, the tongue, palate, oropharynx, and esophagus. Most (75%) of the tumor-bearing animals (TBA) had one AP and only 8% had more than three; in addition, 95% of the TBA had tu at one site and only 5% had them at two sites. Trac farms of origin indicated that TBA could be as old as and as young as 7 mo, that most of the animals did not from upland farms with bracken infestation, and that A be found in both beef and dairy cattle from lowland The four AP sites were identical to those at which carci have been noted in animals from an upland farm are a high alimentary carcinoma incidence. However, the dence of AP, the number of sites involved per anima the number of AP per animal were much higher i high-cancer-area animals, indicating the presence of a plifier of AP, possibly bracken fern. Inclusion bodies, i fied by electron microscopy as viruses, were found in cell nuclei, and a typical papilloma virus was purified the tumors. The histology of the tumors is described, a possible plurality of bovine papilloma viruses is discus the light of recent findings in human viruses. It appea virus-induced AP are widespread in the general cattle p tion but at a low tumor multiplicity. Under certain en mental circumstances, there is an amplification of AP bers and a proportion of animals develop alim carcinoma at the AP sites. The relationship between ing of bracken fern (and other mutagenic and immunosu sive agents) and a variety of isolates of bovine pap viruses in inducing tumors is being studied. (15 refs)

78-5791 **The Occurrence of Human Wart-Virus A dies in Dogs, Pigs and Cattle.** (Eng) Pyrh S. (Lab. Viral Immunopathology, Dept. Virology, Univ sinki, Helsinki, Finland); Neuvonen, E. *Arch Virol* 297-305; 1978.

Dog, pig, cattle, horse, and reindeer sera were screen antibodies against human papilloma virus (wart virus) munodiffusion. Human wart virus antigen was prepare surgically removed skin warts. Antibodies against h wart virus were detected in 28/114 dog sera. Investi of the history of nine dogs showed that two had typical lomas. The prevalance of antibodies increased with th of the dog. The prevalence was similar to, but generally than, that in human children of the same age. A faint p tation line corresponding to that for the antigen was f by 10/97 cattle sera and 5/40 pig sera. No precipitatio seen in 59 horses or 100 reindeer sera. The specificity antibody reaction could also be demonstrated by electr croscopy. For comparison, 50 human sera were studi the presence of bovine papilloma virus antibodies. Nin formed antibodies against a virus proved to be bovine loma virus by electron microscopy. These results questi concept of strict species specificity of the various pap viruses. (23 refs)

78-5792 **Nucleotide Sequence Studies of Polyoma The *Hpa* II 3/5 Junction to the *Hpa* II**

18 Junction, Encoding the Origin of DNA Replication the 5′ End of the Early Region. (Eng) Friedmann, T. pt. Pediatrics, Univ. California, San Diego, CA); La-te, P.; Esty, A. *J Biol Chem* 253(18): 6561-6567; 1978.

nucleotide sequence of polyoma DNA from near the *Hpa* /5 junction to the *Hpa* II 4/*Hae* III 18 junction was ermined by a modified chemical method. The sequence tains 878 base pairs, including the origin of DNA replica- and the region known to encode the hr-t function. The on corresponding to the origin of DNA replication con- s several short repeated sequences and palindromes. ere is a 30-base pair region with striking similarity to the responding region of simian virus 40 (SV40); as in SV40, ortion of that sequence is capable of forming a stable hair- loop. In the region encoding the hr-t function, there is arently a single open reading frame extending from posi- 188 to the *Hpa* II 4/*Hae* III 18 junction. The potential slation product of this open frame begins with an initia- codon starting at position 188, and the first five amino ds of the product are methionine-asparagine-arginine-va- -leucine. This sequence is similar to the NH_2-terminal five ino acids of SV40 small t antigen known from nucleotide amino acid sequencing to be methionine-asparag- -lysine-valine-leucine. Comparison of the nucleotide and ino acid homologies between the early regions of polyoma s and SV40 will shed light on the mechanisms of cell nsformation by these viruses and on the RNA processing nts involved in the biosynthesis of small and large T anti- s. (27 refs)

5793 **Radioimmunoassay of Type D Oncovirus from Continuous J-96 Cells.** (Eng) Vlasenkova, N. K. I. Ivanovsky Inst. Virology, USSR Acad. Medical ences, 123098 Moscow, USSR); Kitsak, V. Y.; Altstein, D.; Zhdanov, V. M. *Acta Virol (Praha)* 22(4): 257-262; 78.

preparation of extracellular J-96 virus (produced by con- uous cultures of human J-96 cells) and an extract of J-96 ls were examined by radioimmunoassay (RIA) for the pre- ce of antigenic determinants of the major internal protein 25) of Mason-Pfizer monkey oncovirus (M-PMV) and in- species antigenic determinants of the major internal pro- n (p30) of murine leukemia virus (MuLV). The J-96 virus eparation replaced ^{125}I-p25 M-PMV almost completely 8%), and the competition curves obtained with M-PMV, 96 virus, and the J-96 cell extract had the same slope. These ta indicate that J-96 and M-PMV have identical antigenic terminants of their major internal proteins, as detected by IA. No group-specific antigenic determinants of p30 MuLV d none of three groups of interspecies determinants charac- istic of mammalian C-type viruses (^{125}I-p30 MuLV-an- p-27 feline leukemia virus; ^{125}I-p30 MuLV-anti-p28 baboon dogenous virus) were detected in J-96 virus or the J-96 cell tract. Failure to detect determinants characteristic of mam- alian C-type viruses may be explained by a lack of perma- nent production of C-type virions by J-96 cells, by the pres- ence of C-type virions in a concentration below the threshold of sensitivity of the RIA, or by the presence of a C-type virus that has no interspecies determinants characteristic of most mammalian C-type viruses. (15 refs)

78-5794 **Morphological Studies of Hamster Brain Cells Transformed In Vitro by a Human Papovavirus BK.** (Eng) Tanaka, R. (Brain Res. Inst., Niigata Univ., 1 Asahimachi, Niigata 951, Japan); Sekiguchi, K.; Ueki, K.; Gilden, D. H.; Koprowski, H. *Acta Neuropathol (Berl)* 41(3): 235-239; 1978.

The morphological characteristics of in vitro BK virus-transformed hamster brain cells (HBBK) were investigated. These cells had a rapid rate of growth and an increased capacity to persist in serial subcultures. HBBK cells were round or polygonal, with a high nucleo-cytoplasmic ratio, marked pleomorphism, and a tendency to epithelial arrangement and multilayered growth. The cells had a round to oval nucleus with numerous nucleoli; mitotic figures and multinucleated cells were frequent. When cell growth was suppressed, the HBBK cells developed long, delicate processes. Specific immunofluorescence for glial fibrillary acidic protein was diffusely distributed in the cytoplasm of almost all HBBK cells. Sc injection of 10^6 HBBK cells into newborn hamsters resulted in poorly differentiated gliomas in 100% of the animals within 4-5 wk. These findings suggest that the virus selectively transformed hamster brain glial cells. (18 refs)

78-5795 **Cleavage Map of BK Virus DNA with Restriction Endonucleases *Mbo* I and *Hae* III.** (Eng) Yang, R. C. (Dept. Biochemistry, Cornell Univ., Ithaca, NY, 14853); Wu, R. *J Virol* 27(3): 700-712; 1978.

The specific cleavage and physical mapping of the DNA of a variant of BK virus BKV(MM), with the use of the restriction enzymes *Mbo*I and *Hae*III are described. *Mbo*I, which recognizes a tetranucleotide sequence, was first used to cleave BKV(MM) DNA to completion. The resulting 10 *Mbo*I fragments were ordered and mapped on the genome by two techniques: *Hin*dIII-*Mbo*I reciprocal digestions of the uniformly ^{32}P-labeled DNA fragments and by *Mbo*I partial digestions of the single-end-labeled *Hin*dIII subfragments. Cleavage of BKV(MM) DNA with *Hae*III produced 21 fragments. Determination of the *Mbo*I sites and the sites from eight other enzymes of BKV(MM) DNA allowed the 21 sites of *Hae*III to be mapped by similar techniques. Even though the BKV(MM) stock contained three species of related viruses, the two techniques allowed the location of the variant DNA to be identified. The region of variation was positioned between map positions 0.64 to 0.71, corresponding to *Hae*III-E. Thus, the specific cleavage map of the 41 sites with their relative positions marked on the genome was constructed. The size of the resultant fragments ranges from 6 to 614

nucleotides in length. At least 80% of the fragments obtainable from the present map are suitable for complete sequence analysis. (24 refs)

78-5796 **Rescue of Infectious Virus from Permissive Monkey Cells Containing Simian Virus 40 DNA Fragments.** (Eng) Moyer, R. C. (Thorman Cancer Res. Lab., Trinity Univ., San Antonio, TX, 78284); Moyer, M. P.; Gerodetti, M. H. *J Virol* 26(2): 272-280; 1978.

Studies were conducted to determine whether defined simian virus 40 (SV40) DNA subgenomes had any detectable biological activity in permissive TC7 monkey cells and whether subviral information could be maintained by the cells in a potentially biologically active form. Permissive cells were separately transfected with SV40 *Eco*RI/*Hap* II A (74% genome) DNA fragments and *Eco*RI/*Hap* II B (26% genome) DNA fragments in the presence of diethylaminoethyl-dextran. Fusion of the cells receiving the A fragment [TC7 (SV40/74) cells], with cells receiving the B fragment [TC7 (SV40/26) cells] resulted in SV40 rescue. TC7 (SV40/74 + 26) cells, which had simultaneously received both complementary subgenomes, either spontaneously produced SV40 upon subculture or yielded virus upon treatment with iododeoxyuridine. Furthermore, fusion of rat cells containing the *Eco*RI/*Hap* II A fragment with TC7 (SV40/26) cells resulted in SV40 rescue. The nature of the released virus was verified by cytopathology, V-antigen production, neutralization, and electron microscopy. No infectious virus was produced when the combinations of cells fused did not total a complete SV40 genome equivalent. (42 refs)

78-5797 **The Relationship of SV40 Replicating Chromosomes to Two Forms of the Non-replicating SV40 Chromosomes.** (Eng) Seidman, M. M. (Dept. Biochemical Science, Princeton Univ., Princeton, NJ, 08540); Garon, C. F.; Salzman, N. P. *Nucleic Acids Res* 5(8): 2877-2893; 1978.

The relationship of the structure of replicating (R) simian virus 40 (SV40) chromosomes (Chr) to the two conformations of the Form I Chr [nonreplicating (NR) SV40 minichromosomes] was investigated by extracting R-Chr and studying them before and after incubation in an in vitro replication system in which replicative DNA synthesis occurs and progeny Form I Chr are generated. R-Chr and NR-Chr were extracted from the nuclei of infected BSC-1 cells using a detergent-free hypotonic buffer soln consisting of 0.5 mM NaH_2PO_4 (pH 7.5), 0.05 M sucrose, and 1 mM dithiothreitol. This procedure produced 20%-30% of the R-Chr with no loss of endogenous Form I DNA during the in vitro replication assays. The R-Chr and NR-Chr were analyzed many times on sucrose gradients. Two forms of the NR-Chr were extracted, one sedimenting at 50S-55S and the other, which had a more compact structure, sedimenting at 80S-85S. The R-Chr sedimented between the two conformations of t ture Chr. Electron microscopy of the R-Chr suggest they replicated in a conformation more closely related 100-A, 55S nucleofilament structure than to the 80S-85S one. Nucleosomes were present on both sides replication forks. In the in vitro assays, all regions SV40 genome were synthesized, and a significant frac the R-Chr completed replication. The progeny Form cosedimented with the 50S-55S Chr, which were prese or to incubation. The sedimentation coefficients and r amounts of the two forms of the mature Chr were una by the incubation. (18 refs)

78-5798 **Human Diploid Lung Fibroblast Cell Li 26 and WI 38 Exhibit Isozyme Shift of A Phosphatase after Viral Transformation.** (Eng) Kna (Institut fur Organische Chemie, Biochemie und Isoto schung, Universitat Stuttgart, Pfaffenwaldring 55 Stuttgart 80, W. Germany); Pfleiderer, G.; Bayreuth *Clin Chim Acta* 88(2): 375-383; 1978.

Immunotitration curves of membrane-associated a phosphatase (AP) revealed that there is a shift from a type of AP cultures of the normal human diploid fib strains WI 26 and WI 38 to placentalike variant after formation of these cells by simian virus 40. This wa firmed by comparing the apparent Michaelis constant heat stability of the AP from the normal and transf cells. Hepatic AP was heat labile and had a Km for p phenylphosphate of about 4.0 x 10^{-4} M. The placental was heat stable and had a Km of about 2.2 x 10^{-4} M transformed cells contained the placentalike form of clusively, which is indicative of an all-or-nothing chan occurrence of the placentalike enzyme is similar to pearance of the placentalike Regan enzyme of AP i human tumors in vivo. The change detected in the formed cells is most likely caused by genetic alterat the cells induced by the transforming virus. (32 refs)

78-5799 **Colony Formation by Simian Virus 40 formed Human Parapharyngeal Cells C in Semisolid Agar.** (Eng) Ruben, R. L. (Dept. Anatom Basic Medical Sciences, Univ. Illinois Medical Cente W. Polk St., Chicago, IL, 60680); Rafferty, K. A. *Cancer Inst* 61(4): 993-1000; 1978.

A human epithelioid cell line (parapharyngeal cells) formed by simian virus 40 (SV40) was tested for its to grow in the absence of an anchoring substrate and phenotypic changes occurring in sublines isolated bec anchorage independence. Line SV-TGo was plated agar medium, and resulting colonies were tested for efficiency in liquid and for virus productivity. After population doublings, the av cloning efficiency of th was 12.3% in liquid and 2.2% in agar, vs 0.002%

negative controls (F2408 rat cells). Agar colonies ap-
ed as spherical aggregates of tightly packed cells (< 0.3-
n), and they were well-dispersed. Twenty-seven subline
nies isolated for transfer to Leighton tubes were identical
e parental line, including epithelioid morphology, organ-
growth pattern, and extreme sensitivity to density-de-
ent inhibition of growth. Seven colonies tested were posi-
for production of infectious SV40 in 14 days. Most
nies grew vigorously and required subculturing in the
19 days. Senescence was noted after 39-44 total popula-
doublings. The ability of this cell line to grow unan-
ed in agar without phenotype change was therefore
onstrated. (36 refs)

800 **Cell-Free Synthesis of Simian Virus 40 T-Antigens.** (Eng) Paucha, E. (Translation Lab., Im-
l Cancer Res. Fund, Lincoln's Inn Fields, London
2A 3PX, England); Harvey, R.; Smith, A. E. *J Virol*
): 154-170; 1978.

in vitro synthesis of two forms of simian virus 40 (SV40)
or antigen (large T and small t) in response to messenger
A (mRNA) isolated from infected CV1 cells was demon-
ed by polyacrylamide gel electrophoresis and tryptic
ide fingerprint analysis of the proteins produced in a
free system derived from L cells and immunoprecipitated
SV40 anti-T serum. The mRNA's for both antigen
s sedimented at about 17.5S, with the mRNA for small
imenting marginally, but reproducibly, ahead of that for
T. Hybridization experiments using *Hae*III fragment
d *Hind*II/II fragment B showed that all fractions active
e cell-free synthesis of the two antigens hybridized equal-
both fragments. This suggests that the mRNA's for
0 T antigens are at least partly virus-coded and that most
he early SV40 mRNA contains sequence information
both ends of the early region. The data suggest that
-T mRNA is spliced. SV40 complementary RNA
NA) was also translated in the L-cell system, and it gave
families of polypeptides that specifically immuno-
ipitated with anti-T serum. The small-t family included
lypeptide indistinguishable by gel electrophoresis and fin-
rinting from small t isolated from cells. The 60K family
a major component of 60,000-mol wt and included other
peptides with mol wts of 14,000-70,000. The 60K family
peptides in common with large T but not small t. The
ides of both families accounted for all the methionine
ides of SV40 large T. It is concluded that small t is proba-
entirely and large T at least predominantly virus-coded,
the small t and 60K families represent the translation
ducts of two different portions of the early region of SV40
A, and that although most, if not all, of the large-T and
ll-t peptides are present in the cell-free product, some
ure of sequence arrangement of SV40 cRNA prevents the
slation of full-length large T and results instead in the
thesis of fragments. The absence of a splice in cRNA is
bably responsible for this result. (57 refs)

78-5801 **Extraction and Fingerprint Analysis of Simian Virus 40 Large and Small T-Antigens.** (Eng) Smith, A. E. (Translation Lab., Imperial Cancer Res. Fund, London WC2A 3PX, England); Smith, R.; Paucha, E. *J Virol* 28(1): 140-153; 1978.

The different forms of simian virus 40 (SV40) tumor antigen (T-ag) isolated from infected CV1 cells by a variety of extraction procedures were analyzed by peptide mapping. In addition, parameters involved in the generation of these T-ag forms were examined. Upon sodium dodecyl sulfate-polyacrylamide gel electrophoresis, the highest mol wt form of T-ag (large T) isolated from CV1 cells comigrated with the large T isolated from SV40-transformed H65-90B hamster cells. Other faster-migrating forms of large T were generated during the extraction by a protease that is active at low pH, but these forms are probably experimental artifacts. After extraction under conditions that minimize proteolytic degradation of large T, a further form of T-ag was isolated. It had a mol wt of 15,000-20,000 and was termed small t. Fingerprint analysis of ^{35}S-methionine-labeled SV40 proteins showed that small t has 10-12 methionine peptides, but large T has 15-18. All but two of the methionine tryptic peptides in small t were also present in large T. Fingerprint data also showed that T-ag's have no peptides in common with SV40 VP1. Reagents that inhibit posttranslational cleavage of encephalomyocarditis virus polyproteins did not affect the synthesis of small t, which suggests that it is not made by proteolytic cleavage of large T in vivo. An alternative model, which proposes that large T and small t are synthesized independently, is discussed in terms of the fingerprint data and the number of methionine tryptic peptides predicted from the primary sequence of SV40 DNA. (43 refs)

78-5802 **Simian Virus 40 DNA Extracted from Infected Cells with Sodium Deoxycholate No Longer Reflects Its In Vivo Superhelix Density.** (Eng) Germond, J. E. (Dept. Biochemistry, Stanford Univ. Medical Center, Stanford, CA, 94305). *J Virol* 26(3): 681-685; 1978.

The superhelix density of simian virus 40 (SV40) DNA was determined using viral DNA extracted from infected African green monkey kidney CV-1 cells with low concentrations (0.25%-0.45%) of sodium deoxycholate (DOC). The superhelix density was reduced compared with that of SV40 DNA extracted from infected cells in the presence of sodium dodecyl sulfate or from purified viral particles; the max reduction was at 0.35% DOC. No reduction was seen after extraction in the presence of 1% DOC. Even at low concentrations of DOC, no minor population of DNA was selected. Up to 0.1% DOC did not prevent the relaxation of SV40 DNA form I by the untwisting extract (UE). The number of nucleosomes of SV40 minichromosomes was reduced in the presence of low concentrations of DOC; histones were extracted from DNA under these conditions. This deproteinization released the nucleosomal constraint imposed on the DNA by the histones, which appeared as superhelical turns susceptible

to UE. When SV40 minichromosomes were incubated with UE in the presence or absence of DOC, the DNA remained fully supercoiled after deproteinization. It is concluded that in the presence of low concentrations of DOC, the nucleosomal structure of SV40 minichromosomes is first damaged by a combined effect of high ionic strength and anionic detergent, allowing the resulting complex to acquire superhelical turns that are then removed by an intranuclear untwisting activity. The DOC-induced changes in the superhelical state of the DNA can be mistaken for its true physiological configuration in the cells. (13 refs)

78-5803 **Discontinuous DNA Replication: Accumulation of Simian Virus 40 DNA at Specific Stages in Its Replication.** (Eng) Tapper, D. P. (Dept. Biological Chemistry, Harvard Medical Sch., Boston, MA, 02115); DePamphilis, M. L. *J Mol Biol* 120(3): 401-422; 1978.

Agarose gel electrophoresis was used to show that replication of simian virus 40 (SV40) DNA molecules is a linear function of the extent of replication from molecules that replicated 15% of the genome to molecules that replicated 95%. This method allowed quantitation of the relative number of DNA molecules throughout replication. SV40 replicating DNA containing uniformly labeled nascent DNA chains was isolated from intact CV-1 celis at the peak of viral DNA synthesis. The DNA pool contained 2.0 ± 0.5 times more 60%-90% replicated molecules than 20%-50% replicated molecules. This asymmetrical distribution did not occur continuously throughout DNA replication, but began with 60%-70% replicated molecules. The late-replicating molecules were found predominantly in a major peak at 89% replication and two smaller peaks at 81% and 79% replication. These results were confirmed by experiments in which viral replicating DNA, briefly labeled with α-^{32}P-deoxycytidine triphosphate (dCTP) in isolated nuclei, was allowed to continue replication in an excess of unlabeled dCTP. The initial distribution of SV40 replicating DNA was similar to that observed in intact cells. Upon continued incubation, 40%-60% of the molecules matured into circular viral DNA by the time DNA synthesis had ceased. Of the replicating DNA molecules that remained, $<$ 10% had not progressed to 50% replication; $>$ 70% of the molecules were at least 80% replicated. The latter molecules had accumulated in two prominent peaks at 89% and 80% replication; a third peak was sometimes seen at 77% replication. DNA was located by measuring the radioactivity in gel slices and by autoradiography. These data demonstrate discontinuities in the rate that DNA replication forks advance as they approach each other to terminate replication. Consequently, SV40 replicating DNA molecules accumulate in at least two or more discrete stages during replication. (50 refs)

78-5804 **Sister-Chromatid Exchange in Virus Transformation (Meeting Abstract).** (Eng) Nichols, W. W. (Inst. Medical Res., Camden, NJ); Bradt, C.; Toji, L. H.; Segawa, M. *Mutat Res* 53(2): 241; 1978. (no refs)

78-5805 **Selective DNA Conservation and Chron Assembly after Injection of SV40 DNA *Xenopus* Oocytes.** (Eng) Wyllie, A. H. (MRC Lab. Mole Biology, Hills Road, Cambridge, England); Laskey, R Finch, J.; Gurdon, J. B. *Dev Biol* 64(1): 178-188; 1978

The fate of simian virus 40 (SV40) DNA injected int nucleus or cytoplasm of *Xenopus laevis* oocytes is descr The cytoplasm degraded all DNA forms; the nuclei degr single-stranded and linear double-stranded DNA, but conserved double-stranded circular DNA in a 55S nu protein complex. The correlation between the efficient scription of SV40 DNA within oocytes and the presen the stable nucleoprotein complex is discussed. (20 refs

78-5806 **Nuclear Viral Transcripts in a Clone of Cells Transformed by SV40.** (Rus) Chum P. M. (Inst. Molecular Biology, Moscow, USSR); Lukan E. M.; Georgiev, G. P. *Dokl Akad Nauk SSSR* 2 984-987; 1978.

The sequence of viral RNA transcription was studied culture of simian virus 40 (SV40)-transformed rat cells (SVRE-17, which contains a single intact copy of DNA). Incubation of highly labeled uncoiled chains of s ic fragments of SV40 DNA with unlabeled nuclear derived from transformed rat cells showed max hybridiz with early DNA fragment (fragment A). (12 refs)

78-5807 **Tumorigenicity and Its Suppression in Cy of Mouse and Chinese Hamster Cell** (Eng) Howell, A. N. (Dept. Molecular Genetics, S Farber Cancer Inst., 44 Binney St., Boston, MA, 02115) er, R. *Proc Natl Acad Sci USA* 75(5): 2358-2362; 197

The effect of cytoplasm on the expression of tumorige was examined with a pair of mouse and a pair of Ch hamster cell lines in intraspecies cybrids formed by recip fusions between either tumorigenic or nontumorigenic and cytoplasms derived from them. With the mouse cell 3T3 and the simian virus 40-transformed line SVT2, th brid clones were tumorigenic when SVT2 cells were with 3T3 cytoplasts, but not in the reciprocal fusion. the hamster cells, CHEF/18 and the spontaneous tra mant CHEF/16, tumorigenicity was partially suppress cybrid clones formed by fusion of tumorigenic CHE cells with CHEF/18 cytoplasts; cybrids were nontumori in the reciprocal fusion. These results indicate tumorigenicity is not cytoplasmically transmitted in two cell pairs, but suppression of tumor-forming ability be cytoplasmically transmitted in the hamster cybrids fact that the cybrids have maintained their suppressed ph types for 20-30 doublings probably rules out the re well-understood gene products, such as messenger R and proteins, as the basis of cytoplasmic suppression. (28

08 **Siderophore-like Growth Factor Synthesized by SV40-transformed Cells Adapted to Picolinic Stimulates DNA Synthesis in Cultured Cells.** (Eng) ndez-Pol, J. A. (Nuclear Medicine Lab., VA Hosp., St. , MO, 63125). *FEBS Lett* 88(2): 345-348; 1978.

mechanism of action of picolinic acid, which induces th arrest in cultured cells, was examined using mutant ines of simian virus 40-transformed BALB/3T3 cells ed to grow in picolinic acid (SVT2Pi3). Medium condi- d by contact with SVT2Pi3 cells contained a highly spe- iron-binding ligand. The material, siderophorelike th factor (SGF), was also produced by SVT2Pi3-A cells, line of SVT2Pi3 cells that multiplies in the absence of n. SGF was characterized as an ionophoropeptide of ap- 1,600 mol wt. SGF stimulated both Fe^{3+} uptake and synthesis in the mutant cells. Therefore, SGF may be mmalian siderophore growth factor that plays an impor- role in the control of DNA synthesis in the mutant cell The results suggest that cellular or extracellular che- like SGF, may have a relevant function as components e transformed cell micronutrient transport system for Fe ther trace metal ions. They also support the hypothesis neoplastic cells produce chelating agents that may be rtant determinants of the uncontrolled growth and inva- ess of transformed cells. (16 refs)

809 **Detection of Mason-Pfizer Monkey Virus Infection by Syncytia Formation of Human Cells ly Transformed by Rous Sarcoma Virus and Simian 40. Brief Report.** (Eng) Ogura, H. (Dept. Virology, er Inst., Okayama Univ. Medical Sch., 2-5-1 Shikata- Okayama 700, Japan); Tanaka, T.; Ocho, M.; Kuwata, da, T. *Arch Virol* 57(2): 195-198; 1978.

an embryonic cells doubly transformed by Rous sar- virus (RSV) and simian virus 40 (SV40) can be used dicator cells for the detection of Mason-Pfizer monkey (MPMV), as they form syncytia upon cocultivation MPMV-producing cells. The cells, named RSb cells, in both the group-specific antigen of RSV and the tumor en of SV40. The cell fusion was blocked by anti-MPMV n, indicating that this phenomenon is MPMV-specific. cells were successfully used for MPMV infectivity assays e same manner as KC (human glioma) cells. Although RSb and KC cells carry the RSV genome, it is not vn if this genome is indispensable for indicator activity. efs)

810 **Temperature-sensitive Mutants of Simian Virus 40. I. Isolation and Preliminary Characterization of B/C Gene Mutants.** (Eng) Noonan, C. A. (Dept. logy and Epidemiology, Baylor Coll. Medicine, Hous- TX, 77030); Butel, J. S. *Intervirology* 10(3): 181-195;

Sixteen temperature-sensitive mutants of simian virus 40 (SV40) were isolated after treatment of wild-type virus with UV light, nitrous acid, or N-methyl-N′-nitro-N-nitrosoguanidine. All of the mutants were assigned to the B complementation group on the basis of quantitative complementation analyses. Characterization of several representative mutants revealed that under restrictive conditions, they produced immunologically identifiable tumor and viral capsid antigens, induced the synthesis of cellular DNA, and replicated infectious viral DNA. In addition, mutant particles produced at 33 C were more heat-labile than wild-type virus. This collection of mutants will be useful in an analysis of SV40 particle morphogenesis. (41 refs)

78-5811 **Chromosome of the Mature Virion of Simian Virus 40 Contains H1 Histone.** (Eng) Nedospasov, S. A. (Inst. Molecular Biology, USSR Acad. Sciences, Vavilov Str. 32, Moscow 117312, USSR); Bakayev, V. V.; Georgiev, G. P. *Nucleic Acids Res* 5(8): 2847-2860; 1978.

Minichromosomes (small free chromosomes) and mature virions were isolated from nuclear extracts of green monkey kidney CV1 cells infected with simian virus 40 (SV40, strain 776), and their protein composition was analyzed by gel electrophoresis (EP). A conventional isolation procedure and a modified one that makes available large amounts of mature virion particles directly from nuclear extracts were used. In the latter, the isolated nuclei of labeled CV1 cells taken at different intervals after infection were extracted with 0.12 M NaCl, 10 mM Na-EDTA, and 10 mM triethanolamine-HCl at pH 8.0 and ultracentrifuged in a sucrose density gradient. The centrifugation time was reduced to 4 hr, which resulted in the appearance of a fast-sedimenting peak containing labeled DNA in addition to the approx 70S peak corresponding to the minichromosomes. Analysis of the protein composition of the virions by sodium dodecyl sulfate-polyacrylamide gel EP in 15% or 5% gels, by acetic acid-urea EP, and by two-dimensional EP revealed the presence of a complete set of histones, including H1. H1 histone was present in the same stoichiometric ratio to the other histones as that in host chromatin. Capsid proteins VP1, VP2, and VP3 were also detected. Virions isolated from nuclear extracts were indistinguishable from those isolated by the conventional method with respect to electron microscopic appearance, buoyant density, and infectivity. The minichromosomes contained all the histones but practically no viral proteins. It is concluded that the SV40 minichromosome is organized in a compact particle of approx 300 A in diameter and that it is incorporated into the virion as a whole, without the loss of any histone fraction. (20 refs)

78-5812 **Differences in the Capacity of Simian Virus 40 (SV40) Tumor Antigens on Cells, Membranes and in Soluble Form to Induce Transplantation Immunity in Hamsters and Mice.** (Eng) Law, L. W. (Lab. Cell Biology,

NCI, Bethesda, MD, 20014); Takemoto, K. K.; Rogers, M. J.; Henriksen, O.; Ting, R. C. *Int J Cancer* 22(3): 315-322; 1978.

The induction of simian virus 40 (SV40) transplantation immunity was compared in BALB/c mice and Syrian hamsters with the use of intact cells, cell membranes and nuclei, and solubilized membranes from several species (mouse, hamster, human, and sheep). All transformed lines were tumor-antigen-positive. The immunosensitive mKSA line of BALB/c mice and the immunosensitive SV34 line of a Syrian hamster were used for tumor challenge. All materials, regardless of source and type of preparation, induced a strong and specific transplantation immunity in the mice, but only SV40 and viable, intact SV34 cells provided protection against tumor cell challenge in the hamsters. In another limited study, BK papovavirus-transformed hamster cells and purified cell membranes and JC papovavirus-transformed hamster cells were immunogenic by the tumor rejection assay in mice but not in hamsters. SV40 immunization did not protect the hamsters against hamster cells transformed by these two viruses. The findings are best explained on the basis that SV40-transformed hamster cells (at least the SV34 cells used here) express a unique tumor-specific transplantation antigen (designated $TSTA_1$), identified by its immunogenicity in the hamster, that is absent from the cells of all the other transformed lines assayed. However, these other transformed lines (ie, mKSA and the human and sheep lines) express another antigen ($TSTA_2$), identified by its immunogenicity in the mouse. Another distinguishing feature is the fact that $TSTA_2$ is relatively stable after cell disruption but $TSTA_1$ is relatively unstable. Therefore, the TSTA induced by SV40 is heterogeneous and comprises at least two antigenic specificities. Explanations of the postulated heterogeneity of TSTA at the molecular level are given. (26 refs)

78-5813 **Epidermal Growth Factor: Relationship Between Receptor Regulation and Mitogenesis in 3T3 Cells.** (Eng) Aharonov, A. (Dept. Biological Chemistry, UCLA Sch. Medicine, Los Angeles, CA, 90024); Pruss, R. M.; Herschman, H. R. *J Biol Chem* 253(11): 3970-3977; 1978.

The time course and concentration dependence of epidermal growth factor (EGF)-induced ^{3}H-thymidine (^{3}H-TdR) uptake and cell division were compared with those required for receptor binding and down regulation (DR) in Swiss 3T3 mouse cells and in simian virus 40 (SV40)-transformed 3T3 cells. Exposure of confluent nondividing 3T3 cells to 10 nM EGF at 37 C resulted in a 70%-85% reduction in the binding capacity for ^{125}I-EGF. This reduction was due to a decrease in the number of available EGF receptors per cell without any change in the affinity of the receptors for EGF (DR). DR was dependent on EGF concentration, temperature, time, and the physiological state of the cell. Receptor loss occurred at physiological EGF concentrations in the range mitogenic for 3T3 cells (0.1-10 nM). Max stimulation of ^{3}H-TdR uptake or cell division occurred at 1 nM EGF, a concentration at which only 20% of the EGF-receptor sites are occupied DR is only 55% complete. Low EGF concentrations nM) resulted in DR of unoccupied EGF receptors. DR o EGF receptors also occurred in SV40-transformed 3T3 In contrast to confluent cells, dividing 3T3 cells rapidl placed EGF receptors on the cell surface in the presen EGF. When EGF was removed from the medium, the receptor was quickly replenished. The initial massive internalization and concomitant receptor DR do not ap to be sufficient for EGF mitogenesis. The major role o reduction of EGF receptors by DR may be to adjust the subsequent sensitivity to EGF. (28 refs)

78-5814 **Molecular Diversity among Five Differen dogenous Primate Retroviruses.** (Eng) Bi M. L. (Lab. Viral Carcinogenesis, NCI, Bethesda, 20014); Sherr, C. J.; Sen, A.; Todaro, G. J. *J Virol* 300-313; 1978.

The endogenous primate viral structural proteins o C-type retroviruses isolated from baboons (M7), mac (MAC-1), and owl monkeys (OMC-1) and of the D viruses isolated from langurs (PO-1-Lu) and squirrel keys (SMRV, M534) were compared biochemically an munologically. Also compared were the polypeptides prototype primate D-type virus of Old World monkeys son-Pfizer monkey virus (MPMV). The RNA genomes C- and D-type retroviruses were unrelated to one anot nucleic acid hybridization criteria, and they coded for u viral structural proteins that could be distinguished b rose gel filtration and polyacrylamide gel electrophores der denaturing conditions. The major structural prot each virus had a distinct primary structure, as determi two-dimensional tryptic peptide analysis, and it was an cally different from the others. The major virion ph proteins of the C-type viruses (pp15) also differed from of D-type viruses (pp13-pp14). Of the three D-type studied, PO-1-Lu and M534 were endogenous to their n tive species, but MPMV, which is transmitted horizo in rhesus monkeys, may have been derived from a vir dogenous to langurs or to a related species. MPM PO-1-Lu contained related RNA genomes and coded tigenically related structural proteins. Although certai oimmunoassays detected interspecies antigenic determ common to the p30 or gp70 proteins of some of these v no one assay detected all groups of endogenous prim troviridae. Data are given that show that, unlike O New World C-type viruses, the three D-type viruses r derived from one set of primordial gene sequences. Th mates contain at least three distinct sets of retroviral two coding for C-type and one coding for D-type virus refs)

78-5815 **Effect of Splenectomy on Herpesvirus Inf and L_2C Leukemia in Guinea Pigs.** (Eng

G. D. (Virology Lab., Veterans Admin. Hosp., West
n, CT, 06516); Gonzalez-Serva, A.; Hastings, K.;
-Cheng, C. K. *In: Advances in Comparative Leukemia*
arch 1977. Proceedings of the VIIIth International Sym-
m on Comparative Research on Leukemia and Related
ses, held in Amsterdam, The Netherlands on 22-26 Au-
1977. Bentvelzen, P.; Hilgers, J.; Yohn, D. S., eds. (New
: Elsevier/North Holland Biomedical Press): 503 pp.;
197; 1978.

nsive hyperplasia, accompanied by high virus titers, was
nt in the spleen of guinea pig herpeslike virus
HLV)-infected Hartley guinea pigs 3 wk postinoculation
thereafter. Removal of the spleen after GPHLV inocula-
reduced the virus titer in the peripheral blood. In addi-
3/9 animals that received a suspension of L_2C leukemia
showed evidence of leukemia in their lymph nodes. The
hanism that permitted development of the leukemia is
clear. (2 refs)

816 ***Herpesvirus ateles* Malignant Lymphoma in Owl Monkeys.** (Eng) Hunt, R. D. (Harvard Medical
, New England Regional Primate Res. Center, 1 Pine Hill
e, Southborough, MA, 01572); Barahona, H.; Daniel, M.
In: Advances in Comparative Leukemia Research 1977.
eedings of the VIIIth International Symposium on Com-
tive Research on Leukemia and Related Diseases, held in
terdam, The Netherlands on 22-26 August, 1977. Bentv-
n, P.; Hilgers, J.; Yohn, D. S., eds. (New York: Elsevier/-
th Holland Biomedical Press): 503 pp.; 198-200; 1978.

ignant lymphomas developed in four owl monkeys inocu-
d im with *Herpesvirus ateles* (titers of $10^{4.5}$ or 10^5/ml of
infectious TCD_{50}). In addition, the virus recovered from
of these monkeys induced lymphomas when reinjected
ree other monkeys. All the animals died or were killed
moribund condition 27-37 days postinoculation. Micro-
ically, the neoplastic infiltrates were confined to the kid-
spleen, lymph nodes, and bone marrow. The liver and
r tissues were spared. Leukemia was not present. (8 refs)

5817 ***Herpesvirus Papio*: A Lymphotropic Herpesvirus of Baboons that is Related to Epstein-Barr
us.** (Eng) Falk, L. (Rush-Presbyterian-St. Luke's Medical
ter, Chicago, IL); Deinhardt, F.; Nonoyama, M.; Schu-
A.; Wolfe, L.; Bergholz, C.; Lapin, B.; Yakovleva, L.;
ba, V.; Henle, G.; Henle, W. *In: Advances in Comparative*
kemia Research 1977. Proceedings of the VIIIth Interna-
al Symposium on Comparative Research on Leukemia and
ated Diseases, held in Amsterdam, The Netherlands on
26 August, 1977. Bentvelzen, P.; Hilgers, J.; Yohn, D. S.,
(New York: Elsevier/North Holland Biomedical Press):
pp.; 201-204; 1978.

oon lymphoblastoid cell lines (LCL) latently harboring a herpesvirus (*Herpesvirus papio*) related to Epstein-Barr virus (EBV) were studied for viral antigen expression, degree of genome homology with EBV DNA (approx 40%), production of transforming virus, and immunologic characteristics. The LCL contained antigens cross-reacting with EBV but lacked detectable Epstein Barr nuclear antigen in anticomplement immunofluorescence tests. Marmoset lymphocytes were transformed in vitro by x-irradiated LCL cells, but not by cell-free supernatants, suggesting little if any production of transforming virus. (8 refs)

78-5818 **Analysis of dCMP Deaminase and CDP Reductase Levels in Hamster Cells Infected by Herpes Simplex Virus.** (Eng) Langelier, Y. (Institut du Cancer de Montreal, Montreal, Quebec, Canada H2L 4M1); Dechamps, M.; Buttin, G. *J Virol* 26(3): 547-553; 1978.

Deoxycytidine monophosphate (dCMP) deaminase, cytidine diphosphate (CDP) reductase, and thymidine kinase (TK) activities were measured in dCMP deaminase-deficient Chinese hamster cells (lA1) or Syrian hamster cells (BHK-21/C13) infected with herpes simplex virus type 1 (HSV-1) or type 2 (HSV-2). Cell cultures were infected at an input multiplicity of 20-50 plaque-forming units/cell. The two viruses enhanced TK and CDP reductase activities in both cell lines, but they did not induce dCMP deaminase activity in lA1 cells or increase the low basal enzyme activity in quiescent BHK-21/C13 cells. In the lA1 cells, TK levels increased 25 times after HSV-2 infection and 10 times after HSV-1 infection; CDP reductase levels, measured only in HSV-1-infected cells, increased 8 times. In the BHK-21/C13 cells, the two viruses resulted in a 25- to 45-fold increase in TK and a 25-fold increase in CDP reductase levels. In contrast to the host enzyme, the virus-induced CDP reductase activity of lA1 and BHK-21/C13 cells was insensitive to inhibition by deoxyATP and deoxythymidine triphosphate. This property should be useful in developing a selection system for HSV-induced CDP reductase activity. (38 refs)

78-5819 **A Host Range Difference Between Herpes Simplex Virus Types 1 and 2.** (Eng) Goldfarb, P. (Inst. Genetics, Univ. Glasgow, Church St., Glasgow G11 5JR, Scotland); Timbury, M. *J Gen Virol* 39(2): 351-355; 1978.

The infectivities of several strains of herpes simplex virus types 1 and 2 (HSV-1, -2) were measured by plating on Chinese hamster lung (Don line) and human fetal lung (HFL) fibroblasts. HSV-1 strain 17 *syn* had a 10^4-fold lower infectivity on Don cells than on human cells; this low infectivity on Don cells was also seen with other HSV-1 strains. Although adsorption and penetration of the virus appeared normal, there was little or no virus eclipse, and viral thymidine kinase was not induced. For all HSV-2 strains tested, the difference in titer between HFL and Don cells was only 10- to 100-fold.

It thus appears that there is a significant difference between the infectivity of HSV-1 and HSV-2 on Don cells. It is not known if this difference is related to antigenic differences between the two serotypes. Four HSV-1 and HSV-2 intertypic recombinants were also tested for infectivity on HFL and Don cells. Three of the four produced differences in titer similar to those observed with HSV-1, but the fourth behaved like HSV-2. (26 refs)

78-5820 **Anatomy of Herpes Simplex Virus (HSV) DNA. X. Mapping of Viral Genes by Analysis of Polypeptides and Functions Specified by HSV-1 x HSV-2 Recombinants.** (Eng) Morse, L. S. (Marjorie B. Kovler Viral Oncology Labs., Univ. Chicago, Chicago, IL, 60637); Pereira, L.; Roizman, B.; Schaffer, P. A. *J Virol* 26(2): 389-410; 1978.

The segregation patterns of polypeptides specified by herpes simplex virus types 1 and 2 recombinants (HSV-1 x HSV-2) were determined and compared with the DNA sequences of the recombinants. HSV-1 and HSV-2 polypeptides with mol wts of 20,000 to 200,000 were enumerated and matched in infected HEp-2 cells. Infected-cell polypeptides (ICP) that underwent rapid posttranslational processing and ICP that varied intratypically in mol wt were identified. Autoradiographic studies of electrophoretically separated ICP revealed that they fell into three groups according to the kinetics of their synthesis. The synthesis of α ICP peaked 2-4 hr postinfection, that of β ICP between 5-7 hr, and that of γ ICP between 12-15 hr. The templates specifying 26 ICP and several viral functions were mapped by correlating their segregation patterns with their DNA sequences. The α ICP mapped at the termini of the L and S components of HSV DNA. Although α ICP mapped entirely within the reiterated sequence of the L component, the template for α ICP 4 appeared to lie only partly within the reiterated sequence of the S component. Cells infected with a recombinant that contains HSV-1 and HSV-2 sequences in the S component produced α ICP 4 of both HSV-1 and HSV-2. Templates specifying β and γ ICP's mapped in the L component and were randomly distributed. Thymidine kinase and resistance to phosphonoacetic acid mapped in the L component. The rapid inhibition of host protein synthesis charactersitic of HSV-2 infections and syncytial plaque morphology were used to map these functions in the L component. Implications of the template arrangements in HSV DNA are discussed. (41 refs)

78-5821 **A Nonlytic Transforming Mutant of Herpes Simplex Virus Type 2.** (Eng) Howett, M. K. (Dept. Microbiology, Milton S. Hershey Medical Center, Pennsylvania State Univ. Coll. Medicine, Hershey, PA, 17033); Rapp, F. *J Med Virol* 2(1): 29-38; 1978.

A previously isolated small-plaque mutant (No. 69) of herpes simplex virus type 2 (HSV-2) strain 333 produces a high ratio of noninfectious to infectious particles when grown nonpermissive temperature (39 C) in hamster embryo lasts (HEF). An attempt was made to take advantage defective nature of this mutant in order to develop a in which cells are transformed by a herpesvirus that been inactivated. The noninfectious particles were te a transformation assay that detects biochemical trans tion by the HSV-specific thymidine kinase (TK) gene. out inactivation, virus particles grown at 39 C in HE were able to transform TK- mouse cells (N clA cl10) infected with an estimated particle input of 2 of the no tious mutant had a transformation frequency of 5 x comparison, cells infected at an original multiplicity o tion of 2 with HSV-2 strain 333, irradiated to yield op transformation, had a transformation frequency of 8 Clones obtained after incubating mutant-infected mou for 3 wk contained herpes-specific antigens, as measu immunofluorescence. The mutant contained a DNA g that had a density identical to the DNA of wild-type Virus and cell DNA synthesis after infection with the at both the permissive (33 C) and nonpermissive temp was similar to that observed in cultures infected w parental virus. Preliminary experiments in which virus grown at 39 C in HEF cells were injected into newbor sters indicate that the virus is not infectious; in addit tumors were produced. (30 refs)

78-5822 **Antibodies to Herpes Simplex Virus Ty Husbands of Patients with Cervical Car (Letter to Editor).** (Eng) Kunkel, M. (Frauenklinik fur Medizinische Mikrobiologie und Epidemiologi helm-Pieck-Universitat, 25 Rostock, E. Germany); der, H.; Gartner, L.; Hofmann, R.; Ratz, K. H.; He *Lancet* 2(8089): 585-586; 1978.

Serum antibodies against the early antigen of herpes virus type 2, as measured by immunofluorescenc found in 43/100 cervical carcinoma patients, 5/50 controls, 10/36 husbands of the patients, and 2/36 ma trols. (4 refs)

78-5823 **Identification of a Herpesvirus Isolate Cytomegalovirus-transformed Human** (Eng) Geder, L. (Dept. Microbiology, Milton S.. H Medical Sch., Pennsylvania State Univ. Coll. Medicin shey, PA, 17033); Hyman, R. W.; Figueroa, M.; O E.; Iltis, J. P.; Dawson, M. S.; Rapp, F. *J Virol* 27(3): 7 1978.

Human embryo lung cells transformed by cytomega (CMV) and transplanted to athymic nude mice yi cytopathic virus, Hershey Medical Center virus (H following prolonged in vitro passage of the tumor ce virus is a double-enveloped herpesvirus, is sensitive t and is inhibited by iododeoxyuridine. No significant a

tionship to herpes simplex virus (HSV) was detected us-
HSV-immune sera in neutralization and immunofluores-
ce tests, but indirect immunofluorescence tests revealed
V-related antigenicity. Further immunological tests re-
ed that HMCV is antigenically indistinguishable from
ctious bovine rhinotracheitis virus. Thus, HMCV appears
e an infectious bovine rhinotracheitis virus, which pre-
ably appeared in the cell culture as a contaminant from
calf serum. (27 refs)

5824 **The Interaction of Hydrocortisone, Lymphoid Cells and Epstein-Barr Virus.** (Eng) Leyritz, M.
pt. Microbiology and Immunology, Ste-Justine Hosp.,
ntreal, P. Q., Canada); Joncas, J. H. *In: Advances in Com-
ative Leukemia Research 1977. Proceedings of the VIIIth
rnational Symposium on Comparative Research on Leu-
ia and Related Diseases, held in Amsterdam, The Nether-
ds on 22-26 August, 1977.* Bentvelzen, P.; Hilgers, J.;
n, D. S., eds. (New York: Elsevier/North Holland Bi-
dical Press): 503 pp.; 209-211; 1978.

ty-one human lymphoid cell lines of various origin were
ted with hydrocortisone (HC: 20 μg/ml) for 3 days and
n examined for cell viability, percentage of Epstein-Barr
s (EBV) antigens, and interferon synthesis. Unlike cell
s derived from the peripheral blood of normal individuals
infectious mononucleosis patients, Burkitt's lymphoma
lines were characterized by a decrease in cell viability,
increase in EBV early antigen-positive cells, and poor in-
eron response. The response of the lymphoma cells to HC
onsistent with the reported in vivo sensitivity of lymphoid
or cells to the lethal effect of glucocorticoids. (7 refs)

5825 **Studies on Epstein-Barr (EBV)-like Viruses of Old World Nonhuman Primates.** (Eng) Rabin,
(Viral Oncology Program, NCI Frederick Cancer Res.
ter, P.O. Box B, Frederick, MD, 21501); Neubauer, R.
Hopkins, R. F. *In: Advances in Comparative Leukemia
search 1977. Proceedings of the VIIIth International Sym-
ium on Comparative Research on Leukemia and Related
seases, held in Amsterdam, The Netherlands on 22-26 Au-
t, 1977.* Bentvelzen, P.; Hilgers, J.; Yohn, D. S., eds. (New
rk: Elsevier/North Holland Biomedical Press): 503 pp.;
5-208; 1978.

man, orangutan, chimpanzee, gorilla, and baboon sera
re tested for antibodies to virus-associated nuclear antigens
human, orangutan, and chimpanzee cells. Of the human
a, 18/26 stained the nuclei of human Raji (B) lymphoid
ls and 2/18 also stained the nuclei of orangutan CP-81 and
mpanzee CH888 cells. Of the orangutan sera, 5/9 stained
ji cell nuclei, 3/5 stained CH888 nuclei, and 2/5 stained
ji cell nuclei. Thus, certain human and orangutan sera con-
n antibodies that cross-react with the nuclear antigens of
se three species. Chimpanzee sera cross-reacted with oran-
gutan antigen but were negative on Raji cell nuclei. Gorilla and baboon sera were negative on all three lines. Baboon virus transformed lymphocytes from several Old World nonhuman primates, but orangutan virus and Epstein-Barr virus from a cotton-topped marmoset line transformed only gibbon lymphocytes. The cells transformed in vitro had the properties of B lymphocytes, and they are being evaluated for possible malignant potential. (10 refs)

78-5826 **Suppression of In Vitro Epstein-Barr Virus Infection: A New Role for Adult Human T Lymphocytes.** (Eng) Thorley-Lawson, D. (Sidney Farber Cancer Inst., Boston, MA, 02115); Chess, L.; Strominger, J. L. *In: Advances in Comparative Leukemia Research 1977. Proceedings of the VIIIth International Symposium on Comparative Research on Leukemia and Related Diseases, held in Amsterdam, The Netherlands on 22-26 August, 1977.* Bentvelzen, P.; Hilgers, J.; Yohn, D. S., eds. (New York: Elsevier/North Holland Biomedical Press): 503 pp.; 219-222; 1978.

The in vitro transformation of human lymphocytes from adult peripheral and fetal cord blood by Epstein-Barr virus (EBV) was studied. B cells from these sources showed similar levels of ^{3}H thymidine incorporation at all times post-EBV infection and showed the same efficiency (100%) and time to outgrowth (13-14 days). However, whole adult peripheral blood lymphocytes required an av of 25 days to grow out. EBV had no effect on the immunoglobulin (Ig)-negative cell population. Reconstitution of lymphocytes to the in vivo ratio of 20:80 B:Ig-negative cells resulted in a marked suppression of B-cell proliferation that occurred early in infection. The suppressor cells were shown to be the TH_1- subpopulation of T cells. The data indicate that the TH_1-T-lymphocyte subpopulation from adults but not fetal cord can suppress the outgrowth of in vitro EBV-infected B lymphocytes. This could reflect in vivo mechanisms involved in recovery from infectious mononucleosis and in the in vivo suppression of EBV-infected lymphocytes harbored by seropositive individuals. (9 refs)

78-5827 **Interaction of Epstein-Barr Virus (EBV) with EBV-Genome-negative, Receptor-positive Human Lymphoid Cell Lines (LCL) Derived from Acute Lymphoblastic Leukemia (ALL) and Lymphoma Patients.** (Eng) Menezes, J. (Dept. Microbiology and Immunology, Pediatric Res. Center, Univ. Montreal, Ste-Justine Hosp., Montreal H3T 1C5, Canada); Patel, P.; Bourkas, A. E. *In: Advances in Comparative Leukemia Research 1977. Proceedings of the VIIIth International Symposium on Comparative Research on Leukemia and Related Diseases, held in Amsterdam, The Netherlands on 22-26 August, 1977.* Bentvelzen, P.; Hilgers, J.; Yohn, D. S., eds. (New York: Elsevier/North Holland Biomedical Press): 503 pp.; 216-218; 1978.

The interaction of Epstein-Barr virus (EBV) with

EBV-genome-negative, receptor-positive human lymphoid cell lines (LCL) derived from patients with acute lymphoblastic leukemia (ALL) or lymphoma was studied. The results indicated that an LCL may bear receptors for only one type of EBV strain and not for the other, suggesting the possible existence of two types of EBV receptors on at least some LCL. An LCL may also express receptors for EBV but not for complement (C′), and an LCL bearing receptors for EBV may prove nonpermissive to EBV infection. These observations relate to a unique and previously unknown type of interaction between EBV and EBV-receptor-positive, genome-negative human LCL derived from ALL and lymphoma patients. It is highly probable that such an interaction also occurs in vivo in man, and it appears to be independent of C′ receptors. (10 refs)

78-5828 **Early Events in Epstein-Barr Virus-induced Transformation of Human Lymphocytes, Studied by Simultaneous Observations of Immunofluorescence, Cellular Morphology and Autoradiography.** (Eng) Takada, K. (Dept. Virology, Cancer Inst., Hokkaido Univ. Sch. Medicine, Sapporo, Japan); Aya, T.; Osato, T. *In: Advances in Comparative Leukemia Research 1977. Proceedings of the VIIIth International Symposium on Comparative Research on Leukemia and Related Diseases, held in Amsterdam, The Netherlands on 22-26 August, 1977.* Bentvelzen, P.; Hilgers, J.; Yohn, D. S., eds. (New York: Elsevier/North Holland Biomedical Press): 503 pp.; 212-215; 1978.

A method for simultaneously observing Epstein-Barr virus (EBV) marker expression, cellular morphology, and autoradiography findings was used to study early events in the transformation of human B lymphocytes by EBV. In human umbilical cord blood B-cell-rich fractions exposed to EBV and then incubated with growth medium containing ^{3}H-thymidine, synthesis of EBV-determined nuclear antigen (EBNA) occurred prior to the blastogenic response and to DNA synthesis. EBNA-positive cells first appeared 12 hr after infection, reaching a max of 17% at 24 hr, whereas blastogenesis became progressively evident after 18 hr and DNA synthesis was noted at 36 hr. In the presence of 10 to 20 μg/ml cytosine arabinoside, EBNA synthesis was observed in 6% of cells in culture 24 hr after EBV infection, at which time EBNA-positive cells were seen in 10% of control infected cultures. Exposure of cells to cycloheximide (10 to 20 μg/ml) for the first 6 hr after infection inhibited EBNA synthesis to one-third of the rate seen in control cultures. Cycloheximide also inhibited morphological transformation. The results indicate that the early events in EBV-induced transformation of human lymphocytes occur sequentially from EBNA synthesis, to blastogenesis, to DNA synthesis. The crucial step in EBNA synthesis and EBV-induced morphological transformation is probably related to certain protein syntheses occurring in the first few hours after EBV infection. (5 refs)

78-5829 **The Epstein-Barr Virus (EBV) in Human thology. II. Serologic Profiles of EBV In tions.** (Eng) Didier, J. (Laboratoire de Bacteriologie-Vir gie, Universite Paul Sabatier, Faculte de Medecine Toulo Rangueil, Chemin du Vallon, 31054 Toulouse Cedex, F ce); Dalens, M.; Chabanon, G.; Icart, J.; Enjalbert, L. *omedicine* 28(1): 54-62; 1978.

Sera from 245 patients, including 139 with infect mononucleosis (IM), were tested for antibodies to stein-Barr virus (EBV) capsid antigen (VCA), early ant (EA), nuclear antigen, and VCA-IgM antibodies. In IM, efficiency of EBV serodiagnosis was lower than that o Paul Bunnel Davidsohn (PBD) reaction. Of the PBD-pos IM patients, only 80% had a serologic profile indicativ primary EBV infection. However, EBV serodiagnosis useful in PBD-negative IM and in benign and malignant phoproliferative diseases. Of the 13 patients with lym proliferative malignancies, almost all were positive for antibodies. In successive sera, these antibodies were frequ ly associated with VCA-IgM antibodies. (41 refs)

78-5830 **Presence of EBNA in Nasopharyngeal cinoma and Control Patient Tissues Relate EBV Serology.** (Eng) Huang, D. P. (Medical and H Dept., Inst. Radiology and Oncology, Queen Eliza Hosp., Kowloon, Hong Kong); Ho, H. C.; Henle, W.; H G.; Saw, D.; Lui, M. *Int J Cancer* 22(3): 266-274; 197

Biopsy specimens from 26 nasopharyngeal carcinoma (N patients, 39 patients with other tumors of the head and the normal nasopharyngeal mucosa of 32 patients in w an NPC had been excluded, and the mucosa from th larged but nonneoplastic tonsils of 12 patients were anal for Epstein-Barr virus (EBV)-associated nuclear antigen NA) by anticomplement immunofluorescence. Blood ples were also taken from the first three patient groups time of biopsy, which was prior to radiation therapy. NA-positive cells were detected in preparations from u ferentiated and poorly differentiated squamous cell provided they contained tumor cell aggregates. These were not detected in two undifferentiated carcinoma pre tions without aggregates and in the only case of well-diff tiated papillary adenocarcinoma. In the head and neck t group, positive cells were found in only three undifferent carcinomas of the nasal fossa. None of the nasophary or tonsillar mucosa preparations contained positive These results confirm the unique association of EBNA undifferentiated and poorly differentiated squamous NPC. In EBV-related serological studies, there was a correlation between titers of IgG and IgA antibodies to capsid antigen and to the diffuse component of early an in patients with undifferentiated and poorly differen squamous cell NPC. Therefore, this simple blood test w be useful in screening for NPC in people with a high r this neoplasm. (33 refs)

831 **Isolation of Epstein-Barr Virus from Cultures of Lymphoblastoid Cells.** (Rus) Zhdanov, V. M. tral Inst. Hematology and Blood Transfusion, Moscow, R); Skorikova, A. S.; Skurkovich, S. V.; Guschin, B. V.; nova, U. A.; Bykovskii, A. F.; Al'shtein, A. D.; Mazuren- N. P. *Probl Gematol Pereliv Krovi* 23(6): 49-55; 1978.

attempt was made to isolate both Epstein-Barr virus V) and oncornavirus from the continuous lymphoblast- cell line L-101 (derived from a patient with acute leuke-). The presence of EBV in the culture was confirmed by tron microscopy and by fluorescence assay: treatment of 01 cells with serum containing antibodies against EBV lted in specific fluorescence that was absent when the were treated with normal human sera. Density gradient rifugation in sucrose gradient revealed a peak of labeled A at 1.24-1.26 g/ml (characteristic buoyant density of esvirus). Although sedimentation in the sucrose gradient showed the presence of ^{3}H-uridine-labeled RNA with a yant density of 1.15 g/ml, data on the persistence of on- avirus in L-101 cells were nonconclusive. (8 refs)

832 **Athymic Nude Mice: Induction of Tumors Containing Epstein-Barr Virus Using kitt's-related Cell Lines.** (Eng) Ablashi, D. V. (NCI, I, Landow Building, Room 9A06, Bethesda, MD, 20014); ser, R.; Easton, J. M.; Nonoyama, M.; Armstrong, G. R. *Hematol* 6(4): 365-374; 1978.

nor development was studied in athymic nude mice inocu- d sc with D98/HR-1 cells (1.0 x 10^6 cells), an epithelial atic cell hybrid containing the Epstein-Barr virus (EBV) ome, or with the parental D98 and HR-1 cells that were ved, respectively, from a human cervical carcinoma and rkitt's lymphoma. The inoculum consisted of cells grown ulture, cells from tumors induced by the cell lines, or cells n tumor-derived cell lines. The D98/HR-1 cells induced ifferentiated carcinomas; the D98 cells, carcinomas; and HR-1 cells, poorly differentiated lymphomas. The num- of EBV genome equivalents was sharply reduced in 8/HR-1 and HR-1 tumor cells, but subsequent in vitro sage of the cells resulted in partial recovery of the EBV ome in HR-1 cells and complete recovery in D98/HR-1 s. Factors influencing EBV genome expression in tumor s are discussed. It is concluded that the nude mouse is a ful model for studying EBV-associated tumors. (30 refs)

5833 **Demonstration of a Surface Antigen on Epstein-Barr Virus Genome-carrying Lymphoid ls: Distinction from the Virus-determined Membrane An- n.** (Eng) Sakamoto, K. (Dept. Microbiology, Kumamoto v. Medical Sch., Kumamoto, 860, Japan); Hinuma, Y. *J munol* 120(5): 1702-1708; 1978.

surface antigen (SA) was detected on Epstein-Barr virus (EBV)-carrying lymphoid cell lines by indirect membrane immunofluorescence with an antiserum from a rabbit immunized with Raji cells. The antiserum had been extensively absorbed with normal human blood and tonsil cells. The SA was not detected on normal human umbilical cord and adult peripheral blood lymphocytes or EBV-negative cell lines. SA is distinct from EBV-determined membrane antigen (MA) as shown by the fact that five cell lines [Raji, NC-37 (C-6), OAT, P3HR-1 (NP), and MAT] that were consistently positive for SA by staining with anti-Raji serum were not stained by anti-MA human serum. Furthermore, HeHR-1 (P) and NHAd-60 lines, known to be positive for MA, were negative for SA. SA was also distinguished from MA in differential absorption tests. The results of cross-absorption tests of antiserum against Raji cells or P3HR-1 cells suggested that SA may contain more than one antigenic determinant. It is suggested that SA is a virally induced but not virally coded antigen. (35 refs)

78-5834 **Interaction of the B95-8 and P3HR-1 Substrains of Epstein-Barr Virus (EBV) with Peripheral Human Lymphocytes.** (Eng) Steinitz, M. (Dept. Tumor Biology, Karolinska Institutet, S-104 01 Stockholm 60, Sweden); Bakacs, T.; Klein, G. *Int J Cancer* 22(3): 251-257; 1978.

The interaction of the B95-8 and P3HR-1 substrains of Epstein-Barr virus (EBV) with normal peripheral blood lymphocytes were explored. B95-8 virus has transforming properties, but P3HR-1 does not. P3HR-1 fails to induce Epstein-Barr nuclear antigen (EBNA) or to stimulate DNA synthesis in normal lymphocytes, although it uses the same receptor for attachment as B95-8. To distinguish between the simple absence of a transforming and DNA-stimulating function and an active inhibition of its host cell, the effect of P3HR-1 pretreatment on subsequent DNA stimulation by B95-8 and by a number of mitogens was studied. P3HR-1 pretreatment completely inhibited the DNA stimulating effect and EBNA induction of subsequently added B95-8. When P3HR-1 was added after B95-8, it diminished DNA stimulation by the latter in a time-dependent fashion. Stimulation of DNA synthesis by the B-cell mitogen *Staphylococcus aureus* was also inhibited by P3HR-1. In contrast, the largely T-cell-stimulating effects of phytohemagglutinin and of an allogeneic mixed lymphocyte culture reaction were uninhibited or only slightly inhibited, which excludes the possibility that P3HR-1 had a nonspecific cytotoxic effect. These results suggest that P3HR-1 inhibits the same lymphocyte fraction that is stimulated by B95-8 and the B-cell mitogen. The effect of P3HR-1 is probably akin to its previously demonstrated growth-inhibitory effect on EBV-receptor-positive lymphoid lines. Early antigen induction is another unique property of P3HR-1, not shown by any transforming virus strain. It is possible that this property is related to the equally unique inhibitory effect of P3HR-1 on host cell DNA synthesis. (33 refs)

78-5835 **Primary Epstein-Barr Virus Infections in African Infants. I. Decline of Maternal Antibodies and Time of Infection.** (Eng) Biggar, R. J. (Dept. Child Health, Univ. Ghana Medical Sch., Accra, Ghana); Henle, W.; Fleisher, G.; Bocker, J.; Lennette, E. T.; Henle, G. *Int J Cancer* 22(3): 239-243; 1978.

Thirty-one newborns in Accra, Ghana, an area endemic for Burkitt's lymphoma, were examined at monthly intervals for the first 15 mo and again at 21 mo to provide basic epidemiologic, clinical, and serologic data on primary Epstein-Barr virus (EBV) infections at an early age. Sera were tested for antibodies to EBV capsid antigen (VCA), EBV-induced early antigen (EA), an EBV-associated nuclear antigen (EBNA) by immunofluorescence techniques and for EBV-neutralizing antibodies and antibody-dependent cell-mediated cytotoxicity. All infants had maternal IgG antibodies to VCA at 1 mo of age and most also had antibodies detected by the other tests, except anti-EA. The anti-VCA titers subsequently declined with a half-life of nearly 5 wk. Depending on initial titers, all infants became seronegative for all antibodies by 2-8 mo, with anti-VCA persisting longest. No seroconversions were noted as long as antibodies to VCA remained measurable or for at least 2 mo after the infants became seronegative. Apparently, maternal antibodies protect infants against primary EBV infections during the first several mo of life. By 12 mo, 44% of the infants had seroconverted; these values increased to 62% and 81% at 15 and 21 mo, respectively. There was no seasonal variation in the incidence of infections. Infants from families of the lowest socio-economic level tended to become infected somewhat earlier than those from higher levels, but no other factors, such as household size or crowding, seemed to be associated with enhanced risk of early infection. Although the route of transmission remains obscure, salivary contact is the most likely source of infection. (24 refs)

78-5836 **Primary Epstein-Barr Virus Infections in African Infants. II. Clinical and Serological Observations During Seroconversion.** (Eng) Biggar, R. J. (Dept. Child Health, Univ. Ghana Medical Sch., Accra, Ghana); Henle, G.; Bocker, J.; Lennette, E. T.; Fleisher, G.; Henle, W. *Int J Cancer* 22(3): 244-250; 1978.

Twenty-six newborns in Accra, Ghana, an area endemic for Burkitt's lymphoma, were examined monthly for 15 mo and again at 21 mo to record clinical, hematologic, and serologic responses during seroconversion (SC). Twelve infants acquired primary Epstein-Barr virus infections (EBV) by 1 yr of age and 9 others seroconverted between 13 and 21 mo of age. The infections were not accompanied by significant signs, symptoms, or hematologic changes that would have suggested a diagnosis of infectious mononucleosis (IM). Only 6/12 seroconverters showed late, minor, or insignificant heterophil antibody (ab) responses. Thus, the primary EBV infections were essentially silent. The 12 early seroconverters showed transient IgM ab responses to EB viral capsid antigen (VCA) that, in some cases, initially exceeded the correspon ing IgG ab's in titer. Peak VCA-specific IgG titers were not 1 mo after SC, and they were comparable to those seen IM. Most infants developed ab's to the EBV-induced ear antigen complex. However, these ab's were directed again the restricted component, as observed in Burkitt's ly phoma, and not against the diffuse component, as noted IM. Low titers of VCA-specific IgA ab's emerged in five i fants. Usually, EBV-neutralizing ab's were already prese in the first anti-VCA-positive serum, but ab's to EBV- sociated nuclear antigen and ab-dependent cell-mediat cytolysis became detectable only months after SC. Attemp to demonstrate EBV by exposure of cord blood lymphocy to filtered throat swab specimens collected from 1 mo befo to 3-5 mo after SC met with limited success, which sugge that there is a low degree of viral excretion during silent S Possible explanations for the differences among clinic hematologic, and serologic respon s to primary EBV inf tions in infancy and later in life are provided. (29 refs)

78-5837 **Hepatitis B Virus DNA in Primary Hepatoc lular Carcinoma Tissue.** (Eng) Summers, J. (F Chase Center, Inst. Cancer Res., Philadelphia, PA, 191 O'Connell, A.; Maupas, P.; Goudeau, A.; Coursaget, Drucker, J. *J Med Virol* 2(3): 207-214; 1978.

Primary hepatocellular carcinomas (PHC) from patients which evidence of past or current infection with hepatiti virus (HBV) existed and from patients in a geographical a in which epidemiological evidence indicates a correlation tween HBV infection and PHC were examined for the pr ence of HBV DNA by nucleic acid hybridization. Specim of tumor, cirrhotic, and metastatic tissue were taken at cropsy from four male Senegalese patients, three of wh were positive for hepatitis B surface antigen (HBsAg). mors from two of these three patients contained HBV D sequences at a level of 1-2 genomes per cell; specimens fr the third patient contained small but detectable amount viral DNA (< 0.1 genomes/10 cells). All three specim from the HBsAG-negative patients contained no detecta HBV DNA. This patient showed evidence of prior HBV fection by virtue of the presence of anti-HBs and anti- core antibody in the serum. The absence of HBV DNA quences in his tumor tissue indicates that the persistence viral genes in every cell is not required to maintain the on genic state of the tumor cells. However, there is no epide ologic evidence that correlates the presence of anti-HBs w PHC in Senegal. (15 refs)

78-5838 **Viral DNA Sequences and Gene Products Hamster Cells Transformed by Adenovi Type 2.** (Eng) Johansson, K. (Dept. Microbiology, Biom cal Center, Univ. Uppsala, Uppsala, Sweden); Persson, Lewis, A. M.; Pettersson, U.; Tibbetts, C.; Philipson, *Virol* 27(3): 628-639; 1978.

nplementary strand-specific adenovirus DNA of full gth or from endonuclease *Bam*HI fragments was used as robe to analyze five LSH hamster cell lines (Ad2HE1-5) nsformed by UV-inactivated adenovirus type 2 (Ad2) for fraction of viral DNA sequences represented and the copy nber of these sequences per diploid equivalent of cellular A. No cell line contained a complete copy of the viral ome, and the fraction present varied from 44% in line 2HE5 to 84% in line Ad2HE3. The number of viral DNA ies per diploid cell equivalent ranged from 1.8 in Ad2HE1 7.1 in Ad2HE4. Serological analyses indicated variation he expression of early viral antigen in all five lines. In vivo eling of cell extracts early after infection with ^{35}S-methio- e followed by immunoprecipitation with specific antisera ealed the presence of virus-specific polypeptides with mol of 42,000-58,000 in all five lines. Several other early viral ypeptides were detected in some of the Ad2-transformed es. Thus, in spite of the presence of large fractions of the al genome in these lines, they demonstrated considerable iation in the number of polypeptides expressed. A hetero- neous class of polypeptides appears to be present in all the es, and it may constitute at least part of the Ad2 tumor igens. (57 refs)

-5839 **Transcription of Viral Genes by RNA Polymerase II in Nuclei Isolated from Adenovirus 2 ansformed Cells.** (Eng) Bitter, G. A. (Dept. Biological emistry, Div. Biology and Biomedical Sciences, Washing- n Univ. Sch. Medicine, St. Louis, MO, 63110); Roeder, R. *Biochemistry* 17(11): 2198-2205; 1978.

n in vitro system was developed that is capable of detecting e synthesis of viral-specific RNA in isolated nuclei from novirus 2 (Ad2)-transformed cells containing several (3-6) tegrated copies of only the left 14% of the adenovirus nome. The α-amanitin sensitivities of the endogenous NA polymerases demonstrated that a class II enzyme tran- ribes the viral genes. The synthesis of viral RNA appeared consist entirely of elongation of RNA chains that were itiated in vivo. Under optimal conditions, the transcription the integrated viral genes was detected by hybridization adenovirus DNA. In nuclei isolated from B1 cells, vi- l-specific RNA represented about 0.01% of the total RNA nthesized in vitro. In isolated nuclei, the synthesis was com- etely (>95%) inhibited by concentrations of α-amanitin .6 μg/ml) that completely and selectively inhibit RNA olymerase II. These results demonstrate the function of an NA polymerase II in the transcription of viral genes in cells ansformed by DNA tumor viruses. The transcription of the ral genes was further analyzed by hybridization of RNA nthesized in isolated nuclei to the purified separated rands of Ad2 DNA. While the stable cytoplasmic viral NA is complementary to only the *r* strand of the viral enome, both strands of the integrated viral genes are tran- cribed. (43 refs)

78-5840 **Evidence for an Adenovirus Type 2-coded Early Glycoprotein.** (Eng) Jeng, Y. H. (Inst. Molecular Virology, St. Louis Univ. Sch. Medicine, St. Louis, MO, 63110); Wold, W. S.; Green, M. *J Virol* 28(1): 314-323; 1978.

Strong evidence that the 20,000- to 21,000-mol wt (20/21 K) polypeptide (pp) induced by adenovirus type 2 (Ad2) in human KB cells is an AD2-coded early glycopolypeptide is presented. The pp could be labeled with ^{3}H-glucosamine, and it bound to concanavalin A (Con A)-Sepharose columns and was eluted with methyl-α-D-mannoside. When labeled with ^{35}S-methionine for short periods (30 min-3 hr), it appeared as a single, sharp band with an apparent mol wt of approx 21K. However, if labeled for long periods or if pulse-labeled and then chased, the pp appeared as multiple bands with apparent mol wts of 20-21K. Partial proteolysis data indicated that the pulse-labeled 21K and the pulse-chase-labeled 20K pp's were highly related, although not identical. Both pulse (30 min) and pulse (30 min)-chase (12 hr in complete minimal essential medium) forms of ^{35}S-labeled 20/21K pp bound to Con A-Sepharose and, therefore, were glycosylated. The 20/21K pp and a 44K pp, labeled with ^{35}S-methionine or ^{3}H-glucosamine in Ad2-infected human cells, were precipitated by rat antiserum against the Ad2-transformed rat cell line T2C4, but not by antisera against three other Ad2-transformed rat cell lines or by serum from nonimmune rats. The partial proteolysis patterns of the 20/21K and 44K pp's were indistinguishable, indicating that the two are highly related and suggesting that the latter might be a dimer of the former. The 20/21K pp was also induced in Ad2-early infected monkey and hamster cells, which implies that the 20/21 K pp is synthesized in Ad2-infected human, monkey, and hamster cells and in one, but not all, Ad2-transformed rat cells. (34 refs)

78-5841 **Purification and Characterization of an Early Protein (E14K) from Adenovirus Type 2-infected Cells.** (Eng) Persson, H. (Dept. Microbiology, Biomedical Center, S-751 23 Uppsala, Sweden); Oberg, B.; Philipson, L. *J Virol* 28(1): 119-139; 1978.

The purification and characterization of an adenovirus type 2 (Ad2) early protein with an apparent mol wt of 14,000 (E14K), as estimated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis, are described. The protein was obtained from infected HeLa cells. Purification involved subcellular fractionation of cytoplasmic extracts, precipitation by dialysis at low pH, and diethylaminoethylcellulose, phosphocellulose, and hydroxylapatite chromatography. The yield was approx 12 μg/10^9 cells. Two Ad2 DNA binding proteins with mol wts of 75,000 and 45,000 were also purified, but tryptic peptide analyses indicated that E14K is unrelated to these proteins. Purified E14K has a high content of basic amino acids and a sedimentation coefficient, in native form, of 5.5S, corresponding to a mol wt of around 95,000.

Pulse-chase experiments suggested that E14K is a primary translation product. Immunoprecipitation with a monospecific antiserum against E14K revealed that it is located exclusively in the cytoplasm of infected cells. Synthesis of E14K began at 2 hr postinfection, and it was max at 4-6 hr postinfection. Immunoprecipitation of cell extracts from four AD2-transformed hamster embryo cell lines revealed that only one expressed this protein. E24K synthesis was not evident in an adenovirus-simian virus 40 hybrid virus, which suggests that the E14K gene is deleted in the genome of this hybrid. (46 refs)

78-5842 **Adenovirus Type 2 Assembly Analyzed by Reversible Cross-linking of Labile Intermediates.** (Eng) D'Halluin, J. C. (Unite de Recherches de Virologie no. 102, Institut National de la Sante et de la Recherche Medicale, Lille, France); Martin, G. R.; Torpier, G.; Boulanger, P. A. *J Virol* 26(2): 357-363; 1978.

Dimethyl-4,4′-dithiobisbutyrimidate dihydrochloride was used as a cleavable cross-linking reagent to maintain the structure of labile intermediates in adenovirus type 2 assembly so that these intermediates could be characterized. Sucrose gradient analysis of nuclear adenovirus particles revealed two size classes, with sedimentation rates of 750S and 600S. After reversible fixation with the diimido ester, the different classes were further separated on CsCl gradients and characterized with regard to their buoyant density, DNA content, and polypeptide composition. The 750S particles banded at 1.345 g/cm^3 in CsCl, contained a DNA with a sedimentation coefficient of 34S in alkaline sucrose gradients, and had a polypeptide composition similar to that of young virions. The 600S population consisted of two types of particles with buoyant densities of 1.315 and 1.37 g/cm^3. The former contained a DNA fragment of 7S-11S and lacked the core proteins V and VII; precursors P VI and P VIII and two nonvirion proteins with a mol wt of 50,000 (50K) and 39K daltons were found in their place. 34S DNA was present in the 1.37-g/cm^3 particles, which also lacked core proteins V and VII as well as the 50K and 39K proteins. Pulse-chase labeling kinetics showed that radioactivity was first detected in the 1.315-g/cm^3 particles, followed by the 1.37- and then the 1.345-g/cm^3 particles. The release of both 50K and 39K proteins was required for entry of viral DNA. (15 refs)

78-5843 **Temperature-sensitive Mutant of Adenovirus Type 2 Blocked in Virion Assembly: Accumulation of Light Intermediate Particles.** (Eng) D'Halluin, J. C. (Unite de Recherches de Virologie no. 102, Institut National de la Sante et de la Recherche Medicale, Lille, France); Milleville, M.; Boulanger, P. A.; Martin, G. R. *J Virol* 26(2): 344-356; 1978.

The assembly of human type 2 adenovirus (Ad2) was studied by biochemical and electron microscopic analysis of different classes of particles obtained with *ts*l12, a temperature-se tive mutant defective in a late stage required for virus matu tion. At restrictive temperatures (39.5 C) this mutant cumulated light precursor particles that were able to mat into infectious virions upon shift of the temperature to 33 A mild extraction procedure and a reversible fixation b cleavable diimido ester were used to isolate the labile in mediates in adenovirus assembly. These particles had a se mentation coefficient of about 600S and a buoyant den of 1.315 g/cm^3 in CsCl. The addition of cycloheximide μg/ml) to a KB cell culture infected with this virus drasti ly reduced the assembly of the precursor particles. The pa cles contained a DNA fragment of 7S-11S and two nonvir proteins with a mol wt of 50,000 (50K) and 39K, respectiv These particles resembled the light intermediate parti found in wild-type Ad2 in both composition and morpholo The wild-type particles were identified as precursors of he intermediates, preceding the young virions. Apparently 112 lesion is located at the exit of either the 50K and/or 3 proteins and at the encapsidation of viral DNA. (32 ref

78-5844 **Tumorigenicity of Adenovirus-5-transfor BHK Cell Lines with Various Transfor tion-associated Properties.** (Eng) Meager, A. (Dept. Biol cal Sciences, Univ. Warwick, Coventry, England); Nairn, Hughes, R. C.; Garrett, A. J.; Reeson, D. E. *Br J Ca* 37(4): 566-570; 1978.

The ability of variant BHK21-C13 cell lines that survi lytic infection with adenovirus 5 to induce tumors in h sters and immunosuppressed mice was determined. transformed cell lines differed in their properties: some a fibroblastic morphology (A1/3 x D, A1/3 x D1), and (F1/3A4) was composed of small round cells early in pass and fibroblasts upon continued culture. Injection of up to normal BHK21-C13 cells into Syrian hamsters produce tumors, but injection of each of the variants produced mors, although at different rates. The tumors grew prog sively to a palpable size usually within 1 mo. Early-pass F1/3A4 cells were less tumorigenic than late-pass F1/3A4 cells and less tumorigenic than the other varia In immunosuppressed mice, normal cells produced tum when $\geq 10^5$ cells were injected sc. The variant A1/3xD more tumorigenic, producing tumors with inocula of cells. Cells derived from tumors produced by lines A1/ D and A1/3 x D1 had the same morphology as the pa cells. Cells derived from tumors produced by F13A4, how er, were predominantly fibroblastic. A1/3 x D- and A1/ D1-derived tumor cells resembled the parent cells in satu tion density and ability to grow in agar suspension or 0. serum. A tumor line obtained by injection of A1/3 x D c into immunosuppressed mice also had the morphology growth characteristics of the parent cells. There was no co lation between expression of a 250,000-dalton protein or er growth-related properties and tumorigenicity in the v ant lines. (8 refs)

845 **Adenovirus-induced Inhibition of Cellular DNase.** (Eng) Nass, K. (Dept. Microbiology and unology, Neil Hellman Medical Res. Building, Albany ical Coll., Union Univ., Albany, NY, 12208); Frenkel,). *J Virol* 26(2): 540-543; 1978.

ogressive decrease in the level of cellular DNase activity rd single-stranded DNA occurred during the productive tion of KB cells by adenovirus type 5 (Ad5). In contrast, level of DNA polymerase remained relatively constant ughout the infection. The decrease could be prevented inhibiting protein synthesis with cycloheximide μg/ml). The inhibition of DNase activity did not ır after infection by Ad5 *ts*125, a DNA-negative ant that fails to induce the adenovirus-specific A-binding protein. In contrast, infection by AD5 , a DNA-negative mutant that complements *ts*125, not result in decreased levels of DNase. It is suggest- that an adenovirus-coded DNA binding protein acts an inhibitor of DNase by binding to the single- nded DNA substrate and thus protects the viral icative intermediates from degradation. (33 refs)

5846 **Adenovirus Type 12 Gene 401 Function in Transforming Infection.** (Eng) Ledinko, N. pt. Biology, Univ. Akron, Akron, OH, 44325). *J Virol* 3): 828-831; 1978.

transforming ability of wild-type adenovirus 12 21WT) was compared with that of the temperature-sensi- *tsTS*401 and *ts*406 mutants using secondary cultures of nster embryo brain (HEB) cells and a cloned rat 3Y1 cell . The *ts*401 mutant was defective in its ability to transform nster and rat cells at the respective nonpermissive temper- res (41.5 and 40 C). The transformation efficiency of WT l *ts*406 at the restrictive temperature was 70% and 90%, pectively, of that at the permissive temperature. The re- ed efficiency of transformation by *ts*401 at the nonpermis- temperature was not due to cell death. At the permissive nperature (38.5 C), *ts*401 transformed HEB cells with six es the efficiency of WT virus, whereas at 41.5 C, the mu- t was defective for transformation compared with WT us. The *ts*406 mutant transformed cells with approx the ne efficiency as WT at both temperatures. The *ts*401 mu- t also had a higher transformation efficiency than WT at C. With 3Y1 cells, there was essentially no difference in clear fluorescent staining characteristics of WT- and mu- t-infected cells at the permissive and restrictive tempera- es. Both mutants also induced cellular DNA synthesis aft- infection of 3Y1 cells at 40 C; *ts*406 was somewhat more icient in this respect than WT or *ts*401. It is suggested that cks of temperature-sensitive mutants may contain a higher portion of transformation-defective genomes than WT us. (15 refs)

5847 **Isozymic Forms of Some Energy Metabolism Enzymes During Oncovirus-induced Cell Transformation.** (Eng) Ageenko, A. I. (Lab. Virology, Hertzen Res. Inst. Oncology, Moscow, USSR); Vitorgan, E.; Gorozhanskaya, G. *Folia Biol (Praha)* 24(2): 128-135; 1978.

Changes in the isozyme spectrum and total activity of hexokinase (HK), lactate dehydrogenase (LDH), and malate dehydrogenase (MDH) that occur during viral carcinogenesis were studied using rat embryo fibroblasts (REF) infected with an oncogenic variant of human adenovirus type 12 (Ad12) or an infectious variant of adenovirus type 6 (Ad6), uninfected REF cultures in different stages of growth, and Ad12-induced hamster sarcoma A12 and rat reticulosarcoma 321-RRS cell cultures. When the REF cultures were infected with Ad6, the activity of HK in the nuclear fraction and cytoplasm was not affected, but those of LDH and MDH were, especially that of LDH-5, which was lost in the cytoplasm. The change appeared as early as the first few days of culture-virus interaction. When the REF cultures were infected with Ad12, however, there were significant changes in all three enzymes in both the nuclear fraction and the cytoplasm. These changes were much more pronounced than those induced by Ad6. It is concluded that both infectious and oncogenic viruses rearrange the isozyme spectrum of the energy metabolism enzymes in the nucleus and cytoplasm, but the latter viruses to a greater degree. Cross analysis revealed changes in HK, LDH, and MDH in the soluble nuclear fraction and cytoplasm of Ad12-infected REF cultures and sarcoma A12 and reticulosarcoma 321-RRS cultures. These changes may serve as objective signs of cell transformation. (16 refs)

78-5848 **Initiation and Termination Sites of Adenovirus 12 DNA Replication II. Analysis of Pulse-labeled Oligonucleotides Derived from 5′ Termini in the DNA Strand.** (Eng) Ariga, H. (Dept. Tumor Virus Res., Inst. Medical Science, Univ. Tokyo, 4-6-1, Shirokane-dai, Minato-ku, Tokyo 108, Japan); Shimojo, H. *Virology* 85(1): 98-108; 1978.

Pulse-labeled oligonucleotides (ON) from the 5′ termini of the adenovirus type 12 (Ad12) DNA strand were studied to determine whether the initiation site of Ad12 DNA replication is located close to or exactly at the 5′ end of the strand. Ad12 DNA pulse-labeled at the initiation site with ^{3}H-thymidine was mixed with U-^{32}P-labeled Ad12 DNA and successively digested with the appropriate endonuclease and exonuclease to leave only the 5′-end ON intact or to digest the 5′-end ON selectively. The ON were separated from the mononucleotides by gel filtration or diethylaminoethylcellulose-Sephadex column chromatography. A temperature-sensitive mutant of Ad12, tsA275, which is defective in the initiation of viral DNA replication at the restrictive temperature, was used in these experiments. The ^{3}H label was not associated with the 5′-end ON of Ad12 DNA when the pulse-labeled DNA was digested completely with spleen DNase II, whereas a significant amount of ^{32}p-labeled Ad12 DNA was mixed with the ^{3}H-DNA as a control. The results

suggest that DNA replication of Ad12 is initiated at a short distance from the 5′ end of the strand. The exclusion patterns of the ON in gel filtration suggest the location of the initiation site to be a short distance (about 20 to 50 nucleotides) from the 5′ end. However, the replication of Ad12 DNA probably terminates right at the 3′ end of the strand. (18 refs)

78-5849 **Analysis of Mammalian Leukemia and Sarcoma Virus *gag* Gene-coded Translational Products: Implications Regarding Sarcoma Virus Structure.** (Eng) Stephenson, J. R. (NCI, NIH, Bethesda, MD, 20014); Reynolds, R. K. *In: Advances in Comparative Leukemia Research 1977. Proceedings of the VIIIth International Symposium on Comparative Research on Leukemia and Related Diseases, held in Amsterdam, The Netherlands on 22-26 August, 1977.* Bentvelzen, P.; Hilgers, J.; Yohn, D. S., eds. (New York: Elsevier/-North Holland Biomedical Press): 503 pp.; 168-170; 1978.

The *gag* gene of mammalian C-type RNA tumor viruses codes for a 65,000-mol wt protein that, upon posttranslational cleavage, gives rise to four virion structural proteins with a mol wt of 30,000 (p30), 15,000 (p15), 12,000 (p12), and 10,000 (p10). Analysis of the intermediate cleavage products isolated from NIH/3T3 cells infected with Rauscher murine leukemia virus (R-MuLV) mutants defective in *gag* gene precursor processing yielded the sequence p15-p12-p30-p10. The *gag* gene expression occurred between the 5′ and the 3′ ends of the viral genome. Independent conformation of the R-MuLV *gag* sequence was obtained by analysis of *gag* gene-coded proteins of cells nonproductively transformed by replication-defective mammalian sarcoma virus isolates. The possibility that sarcoma viruses arise by recombination between leukemia viruses and host genetic sequences is discussed. (9 refs)

78-5850 **Radioimmunologic Characterization of RD-114 Reverse Transcriptase: Evolutionary Relatedness of Mammalian Type C Viral *pol* Gene Products.** (Eng) Krakower, J. M. (Lab. RNA Tumor Viruses, NCI, Bethesda, MD, 20014); Aaronson, S. A. *Virology* 86(1): 127-137; 1978.

The reverse transcriptase derived from the endogenous mammalian C-type virus RD-114 was purified and characterized by biochemical and immunologic techniques. Using radioimmunoprecipitation assays, specific antibodies to reverse transcriptase were detected in the sera of animals naturally or experimentally infected with mammalian C-type viruses. Competition radioimmunoassays using the purified enzyme as a probe detected type-specific antigenic determinants of RD-114 reverse transcriptase, as well as group-specific determinants shared with baboon endogenous virus, the virus to which it was most closely related immunologically. The *pol* gene products of all mammalian C-type viruses were sh to share interspecies antigenic determinants not det among functionally analogous reverse transcriptases of retroviruses. These findings, together with previous munologic evidence, strongly favor a common progenit the evolution of mammalian C-type viruses. (46 refs)

78-5851 **Mutagenic Action of Viruses in Droso (Meeting Abstract).** (Eng) Gershenson, S. Molecular Biology and Genetics, Academy Sciences Ukr an SSR, Kiev, USSR). *Mutat Res* 53(2): 191-192; 1978 refs)

78-5852 **Fine Structure of Viruses of Murine Myelo MOPC-21 and MSPC-1.** (Jpn) Kimura, (Inst. Applied Medicine, Wakayama Medical Coll., Kyu cho, Wakayama 640, Japan). *Saibo* 10(4): 543-546; 197

Both A- and C-type viral particles were detected in mu myelomas MOPC-21 and MSPC-1 by electron microsc The A-type particles were located in the Golgi apparatu the MOPC-21 myelomas, there were > 20 A-type partic tumor and budding was apparent. In the MSPC-1 myelo approx 2-5 A-type particles/tumor were observed unde microscope, and multiple budding was not found. There only a few C-type particles in both tumor strains, and occurred in the extracellular space. Budding was not (7 refs)

78-5853 **Cell-associated Infectivity in the Blood C57Bl Mice Bearing a Radiation-induced kemia (RadVL/D).** (Eng) Baugnet-Mahieu, L. (Dept. R obiology, CEN/SCK, B 2400, Mol, Belgium); Baes, C.; C tier, R.; Maisin, J. R. *Biomedicine* 28(1): 28-35; 1978.

The leukemogenic activity of blood constituents was stu in C57Bl mice bearing a reticulosarcoma of the spleen lymph nodes induced by a radiation leukemia (RadVL/D). Viral C particles could hardly be detected in plasma, and the infectious titer (ED_{50} at 45 d remained very low up to 63 days after inocula Attempts to purify and concentrate a viral fraction infectivity higher than that of crude plasma were successful. From 14 to 63 days post-inoculation, infectious titers of the whole blood, lymphoc and RBC fractions were of the same order of ma tude as that of an extract of lymphoid tissues: 10^2 Because RBC were not involved in the evolution of the ease, care was taken to eliminate possible contaminants (

cytes or adsorbed C particles) from the RBC suspensions. activity of the RBC remained unaltered after differential rifugation on Ficoll/Urografine, sulfoethylcellulose-Sedex chromatography, and trypsinization. Lysis by osmotnock or immune hemolysis always resulted in partial or l loss of biological activity, indicating that to be infectious structure of the RBC must be preserved. As has been cribed for other types of oncornavirus-induced tumors, it ears that blood cells, including RBC and/or their precursors, play a role in the transmission of RadLV/D-induced leukemia. (20 refs)

See also:
*(Rev.): 78-5415, 78-5440, 78-5441, 78-5442, 78-5443.
*(Chem.): 78-5535.
*(Immun.): 78-5864, 78-5865, 78-5866.
*(Path.): 78-5885, 78-5886, 78-5888.
*(Epid.-Biom.): 78-5963.

78-5854 **Enhancement and Metastasis after Immunotherapy of Ovine Squamous-Cell Carcinoma.** (Eng) Jun, M. H. (Dept. Tropical Veterinary Science, James Cook Univ. of North Queensland, Townsville, Queensland 4811, Australia); Johnson, R. H.; Maguire, D. J.; Hopkins, P. S. *Br J Cancer* 38(3): 382-391; 1978.

Ovine squamous cell carcinoma (OSCC) extracts, prepared by different procedures, were inoculated im into 184 OSCC-bearing sheep. At a concentration of 0.5 mg, OSCC protein significantly enhanced tumor growth, and the enhancement increased directly with increasing concentrations of protein. Tumor growth enhancement was associated with increases in metastases in lymphatic vessels draining primary lesions, in local lymph nodes, and in lungs. In control sheep receiving 0.15 M saline-phenol or 3 M potassium chloride extracts containing 3 mg total protein from normal sheep skin, DNA-enriched extracts from human squamous cell carcinoma, or complete Freund's adjuvant alone, tumor growth did not differ significantly from that in inoculated OSCC-bearing sheep. Sheep inoculated with 3 M potassium chloride extract of ovine fetal skin containing 3 mg total protein showed significant tumor growth enhancement and metastasis. All groups inoculated with 0.5 mg or more of tumor protein showed significantly more enhancement of Stage II than of Stage III tumors; no differences in the growth rates of Stage II and III tumors were noted in any of the control groups. The mechanisms involved in the enhancement of OSCC by tumor extracts are not known. (18 refs)

78-5855 **Kaposi's Sarcoma and Immunosuppressive Therapy: An Appraisal.** (Eng) Gange, R. W. (Dept. Histopathology, Inst. Dermatology, St. John's Hosp. Diseases Skin, Lisle St., Leicester Square, London WC2H 7BJ, England); Jones, E. W. *Clin Exp Dermatol* 3(2): 135-146; 1978.

Three male patients (aged, 26, 60, and 78 yr) who developed Kaposi's sarcoma during steroid therapy are compared to 16 others who developed the disease in association with other forms of powerful immunosuppressive treatment. The ages of the 19 patients at the onset of Kaposi's sarcoma were similar to the normal age for development of this tumor, but there was a greater proportion of women (7/19) than is generally observed. Treatments in most cases included steroids, the av duration of treatment being 35.2 mo. Seven of the 19 patients were renal transplant patients. Seven patients, 4 clinically tumor-free, are still alive after an av period of 25.6 mo since diagnosis. Postmortem examination revealed evidence of residual Kaposi's sarcoma in only 5/11 patients. Reducing or stopping immunosuppressive therapy was followed by tumor regression in 3/4 patients. Since spontaneous remission of Kaposi's sarcoma is rare, it would appear to be mor mon in tumors arising as a result of immunosuppress more likely, to be due to a reduction in therapy, thus e ing host resistance. The data support a lymphoid ori the spindle cells of this tumor, which appears to be esp prone to arise as a result of immunosuppressive thera refs)

78-5856 **Role of Intracisternal A-Particles and o Molecules in Plasmacytoma-associate munodeficiency.** (Eng) Katzmann, J. (Section Hema Res., Mayo Clinic/Foundation, Rochester, MN, 5 Bhoopalam, N.; Heller, P.; Hwang, L. T.; Ostro, M.; L D.; Giacomoni, D. *Cancer Res* 38(8): 2555-2561; 197

The origin of the RNA fractions from murine plasmacy (PC's) known to have immunosuppressive activity, th acter of the immunosuppressive RNA molecules, and lationship of these molecules to fractions that induce c in surface immunoglobulins (SIg) were determined. Su lar fractions of the PC's MOPC-300, MOPC-104E, and J558 were transferred sc into normal BALB/c m significantly diminished immune response to sheep R curred in mice given injections of precipitate B. This f copurified with intracisternal A particles. The RNA e ed from precipitate B was also immunosuppressive. T tivity was due to the RNA molecules that contained p nylic acid. Sucrose gradient fractionation showed th RNA populations had immunosuppressive activity: and 40S-50S RNA. The latter population was a therm aggregate of molecules that contained the 12S-18S molecules. In a previous study with normal mous phocytes, PC-derived material with similar physicoch characteristics had induced SIg with the PC idiotyp porting the possibility that one of the mechanisms resp for the development of immunological deficiency is c sion of the SIg of nonmalignant B cells. Apparentl munosuppression and SIg conversion are due to the fractions and molecules. (27 refs)

78-5857 **Correlation of Differences in Antigeni Four 3-Methylcholanthrene-induced Tum Syngeneic Mice with the Susceptibility of Tumors to munopotentiator, PS-K.** (Eng) Abe, S. (Faculty maceutical Sciences, Univ. Tokyo, Hongo 7-3-1, Bunk Tokyo 113, Japan); Yamazaki, M.; Mizuno, D. *Gann* 223-228; 1978.

The growth inhibitory effects of the immunopote PS-K on syngeneic 3-methylcholanthrene-induced tum

DDD mice were compared with differences in an-
icity among the tumors. Mice were immunized by im-
tation of tumor fragments in the tail, after which the tail
amputated. Two weeks later, immunized and control
were challenged with 1.0 x 10^6 cells from the same tu-
The ratios of the tumor diameters of the immunized to
rol mice indicated that the original MSC-1 and MCA-4
ors had high antigenicity, MCA-DDD and MCS-5 had
rmediate antigenicity, and MCS-3, MCS-7, and MCS-9
low antigenicity. MCS-8, MCS-6, and MCS-10 may have
high antigenicity. Immunization with MCS-1 or MCS-8
pletely inhibited tumor growth following challenge,
reas immunization with MCS-9 did not inhibit
or growth after challenge at any dose. MCS-1 and
S-8 thus appeared to be highly antigenic and MCS-
ppeared to be weakly antigenic. Mice immunized
1 MCS-1 or MCS-8 were not resistant to challenge
1 MCA-DDD, indicating that the tumor resistance
tumor-specific. The effect of PS-K on the growth
these tumors was significantly correlated with their
genicity, but there was no significant correlation
veen antigenicity and the effect of the mitotic poison,
ercaptopurine, on tumor growth. The data suggest that
antitumor activity of PS-K may be used as an indicator
ntigenicity in an experimental system. (12 refs)

5858 **Further Studies on the Tumor-specific Suppressor Cells Induced by Ultraviolet Radiation.**
g) Fisher, M. S. (Cancer Biology Program, NCI Frede-
Cancer Res. Center, Frederick, MD, 21501); Kripke, M.
J Immunol 121(3): 1139-1144; 1978.

dence that suppressor lymphocytes are present in
-irradiated mice is given, along with the characteristics
specificity of these cells. Specific pathogen-free mice of
inbred strains C3H/HeN(MTV-)(C3H-) and C57BL/6N
) were UV-irradiated with sun lamps that delivered an av
e rate of 2.8 joules/m^2/sec over the wavelength range
-340 nm. Dorsal hair was removed 1 x/wk, and mice were
adiated for 1 hr, 3 x/wk, for a minimum of 3 mo. Lymph
des and spleens from normal and UV-irradiated mice were
noved, cell suspensions were prepared, and lethally
rradiated mice were inoculated with 5 to 10 x 10^7 lymphoid
ls (LC's). Reconstitution of lethally x-irradiated mice with
's from syngeneic UV-irradiated donors failed to confer
otection against challenge with a syngeneic UV-induced
nor, whereas reconstitution with LC's from normal donors
s protective. When LC's from UV-irradiated mice were
xed with normal LC's before transfer, the recipients were
ain unable to resist tumor challenge, and it was shown that
's from UV-irradiated donors actively suppressed the re-
onse of normal LC's. Furthermore, the suppressor LC's
re enriched after incubation on nylon wool columns, they
re inactive after treatment with anti-θ serum and comple-
ent, and they were effective for at least 7 wk after transfer
lethally x-irradiated mice. Splenectomy of UV-irradiated
ice before tumor challenge did not restore their antitumor
activity. The UV-induced suppressor cells appeared to be specific for syngeneic UV-induced tumors, since they did not suppress the rejection of an allogeneic UV-induced tumor or two chemically induced syngeneic tumors. (21 refs)

78-5859 **Tumor Specific Fluorescent and Complement-Dependent Cytotoxic Antibodies in the Serum of Rats with Chemically Induced Brain Gliomas.** (Eng) Stavrou, D. (Lehrstuhl fur Allgemeine Pathologie und Neuropathologie, Institut fur Tierpathologie der Ludwig-Maximilians-Universitat Munchen, Veterinarstrasse 13, D-8000 Munchen 22, E. Germany); Anzil, A. P.; Elling, H. *Acta Neuropathol (Berl)* 43(1-2): 111-117; 1978.

The biologic activity of antibodies in the sera of Sprague-Dawley and Long-Evans rats with N-methyl-N-nitrosourea-induced gliomas was investigated using a fluorescent antibody staining method and a complement-dependent microcytotoxicity assay. Of the chemically induced tumors, a mixed glioma, an astrocytoma, and an oligodendroglioma were established in vitro, and the first two were successfully cloned. Specific antibodies in the sera of rats with primary brain tumors were determined using the cultured cells as targets. Fluorescent and cytotoxic antibodies were demonstrated in the sera of the mixed glioma- and astrocytoma-bearing animals. However, a variable proportion of the cloned cell lines showed no reaction with the corresponding sera, and cytotoxic antibodies had a lytic effect on the autologous glioma cells only in the presence of rabbit complement. The data suggest that some cells in chemically induced tumors have antigenic properties and others do not. (15 refs)

78-5860 **Lymphocytes in Ataxia Telangiectasia: Implications of the DNA Repair Defect.** (Eng) Lavin, M. F. (Dept. Biochemistry, Univ. Queensland, Brisbane 4067, Australia); Kidson, C. *Clin Immunol Immunopathol* 10(3): 325-329; 1978.

The DNA repair capacity of phytohemagglutinin (PHA)-stimulated lymphocytes from four patients with ataxia telangiectasia (AT) and 11 healthy individuals was investigated after the cells were exposed to ionizing radiation. At radiation doses up to 50 krads, there was a 6- to 10-fold reduction of repair synthesis in AT lymphocytes compared with control lymphocytes. The marked impairment of repair observed in PHA-stimulated lymphocytes from AT patients provides a suitable and rapid clinical laboratory assay for AT homozygotes. The high incidence of tumors in AT homozygotes could be related to both a generalized DNA repair defect per se and to the associated lymphocyte defect if the latter results in decreased immune surveillance. (16 refs)

78-5861 ***Corynebacterium parvum* Enhances Colonic Cancer in Dimethylhydrazine-treated Rats.**

(Eng) Cruse, J. P. (Surgical Unit, Univ. Coll. Hosp. Medical Sch., University St., London WC1E 6JJ, England); Lewin, M. R.; Clark, C. G. *Br J Cancer* 37(4): 639-643; 1978.

The effect of *Corynebacterium parvum*, a bacterial vaccine used as immunotherapy following surgery for colorectal cancer in humans, on dimethylhydrazine (DMH)-induced colon tumors in female Wistar rats was determined. The rats were divided into four groups: Group A received DMH 20 mg/kg/wk for 20 wk; Group B received DMH + *C. parvum* (4 doses, 3.5 mg ip) at weeks 13, 16, 19, and 22; Group C received only *C. parvum*; and Group D received saline (1 mg/kg/wk, sc). *C. parvum* was first administered 13 wk after the first DMH injection to provide a population of activated macrophages at a time when the colonic epithelial cells are known to show abnormal morphological changes. All Groups C and D animals were alive at 36 wk. Group B animals had a significantly increased mortality compared with Group A animals. All Groups A and B animals examined postmortem had malignant colonic tumors, but Group B showed earlier signs of tumor presentation, greater numbers of tumors per animal, and a greater incidence of metastases than Group A animals. The extent and incidence of metastases were striking, since metastases are generally rare in this model system. Furthermore, 4/9 Group B animals developed primary cancers at sites other than the intestine (ie, squamous cell carcinomas of ear canal). The mechanism by which *C. parvum* enhances cancer in this model system is not known. (33 refs)

78-5862 **Lung Tumor-associated Derepressed Alloantigen Coded for by the *K* Region of the *H-2* Major Histocompatibility Complex.** (Eng) Gipson, T. G. (Div. Virology, Bureau Biologics, Dept. Health, Education, and Welfare, Food and Drug Admin., Bethesda, MD, 20014); Imamura, M.; Conliffe, M. A; Martin, W. J. *J Exp Med* 147(5): 1363-1373; 1978.

The strain and tissue distribution of the lung tumor-associated alloantigen that induces radioresistant immunity against lung tumor 85 in C3Hf mice was studied. Lung, liver, and kidney tissues from strain A and C3H mice and spleen cells of (C3HF x A)F_1 mice evoked radioresistant anti-lung tumor immunity in C3Hf mice; no tissue from C3Hf mice provided antitumor protection. C3Hf mice were also protected by preimmunization with 15-day C3H embryo tissue but not by C3Hf embryo tissue. Mice that shared the *H-2a* haplotype with strain A mice or the *H-2k* haplotype with C3H mice induced highly significant immunity in C3Hf mice; tissue from mice with other *H-2* haplotypes was not effective. The gene coding for the expression of the alloantigen was therefore linked to the major histocompatibility complex (MHC). The haplotypes common to all strains conferring antitumor immunity were *H-2Kk* and *H-2IAk*. Anti-lung tumor immunity was not induced by tissue from A.TL (*H-2Ks*) or B10.AQR (*H-2Kq*) mice, and immunity was not conferred in C3H mice by tissues from the strains that induced immunity in C3Hf mice. The finding of a tumor-associated c in the expression of an *H-2K* region-coded antigen is c ent with the concept that MHC-coded antigens may targets for the immunological surveillance of tumor refs)

78-5863 **An Association Between Actin and the Histocompatibility Antigen H-2.** (Eng) G. L. (Medical Res. Council, Lab. Molecular Biology, Rd., Cambridge, England); Smith, M. J. *Nature* 273(274-278; 1978.

P815 cells, a murine mastocytoma, shed large amou plasma membrane-derived material (exfoliate), in which is the major protein. The exfoliate also contain the histocompatibility antigen H-2. The association betwe tin and H-2 is stable even in the presence of detergen dicating that the association depends solely on protei tein interactions. The close parallel in the rates and e of shedding of H-2 and actin and the absence of acti H-2 in the exfoliate argue against the possibility tha come together after the shedding. It is therefore assume the H-2-actin association exists in the cell before the e tion occurs and that studies on the isolated H-2-actin plex are likely to be relevant to the arrangement of the ponents in the intact cell. (35 refs)

78-5864 **Common Antigens Found on Fetal Cells a ral Transformed Adult Prostatic Tissue.** Javadpour, N. (Surgery Branch, Building 10, Room 10 NCI, Bethesda, MD, 20014); Hyatt, C. L.; Barone, J *Surg Oncol* 10(3): 245-250; 1978.

A study was conducted to examine the immunologic sim ty of hamster fetal antigens to antigens expressed on s virus 40 (SV40)-transformed hamster prostatic tissue a assess the protection conferred on the adult host by feta immunization against growth of the virally induced t plantable prostatic tumor. Immunization with fetal a significantly decreased the incidence of tumor growth 60% to 0%. Complement-dependent humoral cytotoxic target SV40 tumor cells in microtest plates was used to onstrate the presence of significant antibody titer i al-immunized hamsters. When the immune sera wer sorbed with SV40-transformed prostatic tissue, cytoto indices were markedly lower than those of the unabs immune sera. The transformed prostatic tissue had an e ed tartrate-inhibited acid phosphatase activity indicati the presence of epithelial components in the transforme sue. These results demonstrate in vivo and in vitro cross- tivity between fetal antigens and tumor associated ant of transformed prostatic tissue, and they suggest that is a similarity between fetal antigens and antigens of a sp organ tissue (prostate) transformed by a DNA onco virus. (11 refs)

5865 **Human Leukemia Associated Antigens (HLAA) on Cells from an AML Patient (HL23) and on ue Culture Cells Infected with HL23 Virus (HL23V) and nate Oncornaviruses.** (Eng) Metzgar, R. S. (Dept. Mi-biology and Immunology, Duke Univ. Medical Center, rham, NC, 27710); Mohanakumar, T.; Gallagher, R. E. *Advances in Comparative Leukemia Research 1977. Pro-dings of the VIIIth International Symposium on Compara- Research on Leukemia and Related Diseases, held in Am-dam, The Netherlands on 22-26 August, 1977.* Bentvelzen, Hilgers, J.; Yohn, D. S., eds. (New York: Elsevier/North lland Biomedical Press): 503 pp.; 371-374; 1977.

tured and uncultured cells from a patient (HL23) with te myelogenous leukemia (AML) were tested for their ctivity with cytotoxic primate antisera to human leu-nia-associated antigens (HLAA). The cells did not react h antisera to chronic lymphocytic leukemia (CLL) or te lymphoblastic leukemia, but they did react with antis- to AML. Two tissue culture cell lines (CCL 88, derived m bat lung, and A204, derived from a human rhab-myosarcoma) were nonreactive with the antisera until they re infected with secondary virus isolates (HL23V) from L23 cells. The antigenic reactivity of the secondarily infect-cells differed from that of the cultured and uncultured cells m patient HL23. A204 and CCL 88 cells infected with boon endogenous virus (BaEV) did not react with simian tisera to CLL but did react with antisera to myeloid cells. e reaction pattern of the BaEV-infected cells was similar that seen after HL23V infection; however, it differed arkedly from that of A204 and CCL 88 cells infected with nian sarcoma virus or gibbon ape lymphoma virus. The use secondarily infected cell lines offers a new approach to ndying the nature of the cross-reactivity between simian tisera and HLAA. (8 refs)

-5866 **Expression of Oncofetal Antigens on Murine Sarcomas Characterized for Expression of En-genous MuLV.** (Eng) Pollack, S. B. (Fred Hutchinson ancer Res. Center, 1124 Columbia St., Seattle, WA, 98104). *t J Cancer* 22(3): 344-350; 1978.

Methylcholanthrene (3-MC)-induced BALB/c mouse fi-rosarcomas previously characterized for the expression of ndogenous murine leukemia virus (MuLV) were tested for e presence of oncofetal antigens (OFA) using rabbit an-serum to day 10-14 BALB/c fetuses. Iodinated protein A om *Staphylococcus aureus* was used to quantitate binding f the antiserum to cultured tumor or fetal cells or to saline xtracts of tumors and fetuses. After absorption in vitro with ormal adult mouse tissues and in vivo in adult mice, the ntiserum bound to cells or extracts of fetuses and sarcomas o varying degrees but not to endogenous MuLV (BALB irus 1). This indicates that OFA on 3-MC-induced sarcomas xist as serologically recognizable antigens distinct from MuLV antigens. The anti-OFA activity of the serum could e absorbed with fetal cells and could be competitively inhib-ited by fetal extract but not by an extract of adult BALB/c lungs or by bovine serum albumin. The serum bound to some but not all lines known to express MuLV. The antiserum bound equally well to MuLV-negative and MuLV-positive sublines of the 3-MC-induced sarcomas 1420 and 1414 but not to Moloney sarcoma cells and the 3-MC-induced sarcoma 1386. Thus, the absorbed antiserum detects a class of common cross-reacting antigens that are serologically distinct from MuLV-associated antigens. (19 refs)

78-5867 **Effect of Embryonic Tissue Immunization on Chemically Induced Gastrointestinal Tumors in Rats. I. Can Embryonic Antigens Act as Rejection Antigens?** (Eng) Bansal, B. R. (Dept. Surgery, Alma Dea Morani Lab. Surgical Immunobiology, Medical Coll. Pennsylvania, 3300 Henry Ave., Philadelphia, PA, 19129); Mark, R.; Rhoads, J. E.; Bansal, S. C. *J Natl Cancer Inst* 61(1): 189-201; 1978.

The relationship of antigens shared by embryonic tissue and 1,2-dimethylhydrazine dihydrochloride (DMH)-induced primary gastrointestinal (GI) tumors was studied in inbred WF rats. The rats were inoculated with crude suspensions prepared from liver and gut tissue of 12- to 15-day fetuses of the same strain. Rats previously unsensitized to syngeneic embryonic tissue were inoculated with fetal material sc three times during DMH administration (15 mg base/kg/wk sc, in 2 divided doses). The optimal time period for immunization was when $<$ 30 mg of the total DMH had been administered; ie, prior to the development of microtumors in the GI tract. Properly timed immunization inhibited the development, growth, and metastasis of primary GI tumors. The effect was observed in both sexes, but it was more pronounced in male rats. Seven of nine WF rats with DMH-induced carcinomas of the GI tract rejected syngeneic embryonal tissue implants, demonstrating the presence of a concomitant immune response to embryonic antigen(s). The two rats in which fetal tissue grew out to palpable nodules had multiple GI tumors with metastasis and extra-GI tumors, ie, a massive tumor load. Ten other rats with DMH-induced GI tumors displayed a delayed hypersensitivity reaction to embryonic antigens after being treated with unblocking serum and inoculated id with syngeneic fetal tissue. These results indicate that embryonic antigens common to fetal and tumor cells can induce immunity in an autochthonous host and can act as rejection antigens. (41 refs)

78-5868 **The Isozyme Pattern of Cyclic AMP-dependent Protein Kinase and the Distribution of a Cervicovaginal Antigen in Experimental Carcinoma of the Cervix Uteri of Mice.** (Eng) Doskeland, S. O. (Inst. Anatomy, Univ. Bergen, Arstadvei 19, 5000 Bergen, Norway); Kalland, T.; Breistein, L. S.; Fossberg, T. M.; Ueland, P. M. *Acta Pathol Microbiol Scand (A)* 86(2): 121-130; 1978.

Tissue sections from 12 3-methylcholanthrene-induced carcinomas of the cervix uteri of mice were tested for the presence of an antigen normally confined to the cervicovaginal epithelium. The antigen was detected in 10/12 tumors examined by indirect immunofluorescence and in all 7 tumors examined by the more sensitive method of mixed hemagglutination. The concentration of the antigen was generally higher in the well-differentiated areas of the tumors, but it was also found to be associated with solitary tumor cells that apparently were invading the stroma. The presence of cervicovaginal antigen in the tumors suggests that tumor cells originated from the cervicovaginal epithelium. The cyclic AMP-dependent protein kinase in the tumor cytosols was studied by chromatography on agarose and diethylaminoethylcellulose. The enzyme had the same properties as those of normal vaginal epithelium. Thus, the tumor cells contained an apparently normal complement of this enzyme, which is believed to be responsible for most of the intracellular action of cycl AMP. (36 refs)

See also:
*(Rev.): 78-5438, 78-5439, 78-5440, 78-5443, 78-54 78-5462.
*(Chem.): 78-5499, 78-5520, 78-5524, 78-552 78-5527, 78-5531, 78-5538, 78-564
*(Phys.): 78-5722, 78-5728.
*(Viral): 78-5740, 78-5748, 78-5749, 78-5754, 78-575 78-5763, 78-5769, 78-5774, 78-5779, 78-578 78-5785, 78-5786, 78-5789, 78-5791, 78-581 78-5815, 78-5825, 78-5828, 78-5830, 78-583 78-5834, 78-5835, 78-5836.
*(Path.): 78-5888, 78-5895, 78-5896.
*(Epid.-Biom.): 78-5920, 78-5940.

5869 **Familial Intraocular Malignant Melanoma. A Case Report.** (Eng) Green, G. J. (Oncology Sec-, Medical Service, Boston Veterans Admin. Hosp., 150 Huntington Ave., Boston, MA, 02130); Hong, W. K.; Ev-t, J. R.; Bhutani, R.; Amick, R. M. *Cancer* 41(6): 1-2483; 1978.

Family with multiple malignancies, including intraocular lignant melanoma (IMM), is described. Both the 50-yr-old band and his father had IMM of their left eyes. A third eration was probably involved, since the proband's pater- grandmother had an eye enucleated because of a tumor ner 50's. The relationship of IMM to multiple malignancies discussed. (20 refs)

-5870 **Segregation of Chromosome 13 in Retinoblastoma (Letter to Editor).** (Eng) Knight, L. A. iv. Cytogenetics, Dept. Pathology, Toronto General osp., Toronto M5G 1L7, Canada); Gardner, H. A.; Gallie, L. *Lancet* 1(8071): 989; 1978.

family in which the mother and one of two living children d retinoblastoma was examined karyotypically to deter-ine if chromosome 13 was associated with the retinoblas-oma. The two children had inherited different maternal romosomes 13, suggesting that the child with retinoblas-oma had inherited it from her mother via this chromosome. ne other karyotypic examination was not performed on a ird child who had died of malignant retinoblastoma at the ge of 3. (3 refs)

8-5871 **Duplication of the Long Arm of Chromosome 1 in a Malignant Vaginal Tumour.** (Eng) Atkin, N. B. (Dept. Cancer Res., Mount Vernon Hosp., Northwood, Middlesex, England); Baker, M. C. *Br J Cancer* 38(3): 68-471; 1978.

Chromosome studies were performed on metaphase speci-mens of an anaplastic, malignant, small round cell tumor removed from the vagina of a 68-yr-old nulliparous woman. Ten years previously, she had undergone surgery for a well-differentiated endometrial adenocarcinoma; no chemotherapy or radiotherapy had been given. A total of 26/34 metaphases had 47 chromosomes; 1 had 49, 1 had 48, 4 had 46, and 2 had 45 chromosomes. G-banded preparations and karyotypic analysis of 5 metaphases with 47 chromo-somes suggested an additional chromosome resembling chromosome 1 in length and centromeric position, but with an abnormal pattern on its short arm. The metaphase with 48 chromosomes differed only in having an additional chromosome 10; that with 49 had an additional C-group and chromosome 3. The abnormal chromosome was present in at least one of 46-chromosome metaphases, which had only one normal chromosome 1. C banding showed that, of the two normal and one abnormal chromosomes 1, two had a pericentric inversion of the heterochromatic region. These findings, combined with previous ones, suggest that a chromosomal imbalance resulting from excess critical gene loci on the long arm of chromosome 1 plays an important role in determining the neoplastic properties of malignant tumors cells. (9 refs.)

78-5872 **Mixed Intracranial Sarcomas: Rare Forms and a New Association with Previous Radiation Therapy.** (Eng) Averback, P. (Dept. Pathology, Univ. Cambridge, Tennis Court Road, Cambridge CB2 1QP, England). *Ann Neurol* 4(3): 229-233; 1978.

The first two cases of mixed sarcoma-glioblastoma with a history of irradiation to the head are reported. Both occurred within 1 yr of radiation therapy for pituitary adenoma and residual meningioma, respectively. In addition, two unique variants of brain mixed sarcomas with marked tumor metaplasia are described, and problems concerning the origin of mixed-population brain tumors are listed. (43 refs)

78-5873 **Melanoma in a Patient Treated for Psoriasis.** (Eng) Durkin, W. (Univ. Alabama, Univ. Station, Birmingham, AL, 35294); Sun, N.; Link, J.; Paroly, W.; Schweitzer, R. *South Med J* 71(6): 732-733; 1978.

The development of melanoma in a 32-yr-old white man who had been treated for psoriasis for 20 yr is discussed. Generalized psoriasis was diagnosed at age 12, and the patient was treated with a variety of regimens, including coal tar and UV light. At age 32 a polypoid, invasive melanoma was diagnosed. During the next 2 yr, metastasis to the right axillary node and left lung was observed. This is the only case of melanoma occurring in a patient treated for psoriasis reported in the world literature. (19 refs)

78-5874 **Liver Tumors and Oral Contraceptives.** (Eng) Ansari, A. H. (Atlanta Fertility Inst., Baptist Professional Building, Suite 641, 340 Boulevard, N.E., Atlanta, GA, 30312); Ravry, M. J.; Stanton, P. E.; Hanafi, M. *Fertil Steril* 29(6): 643-650; 1978.

Three cases of hepatocellular adenoma are reported that support the existence of an association between these tumors and oral contraceptive usage. The three women, aged 25, 48, and 37 yr, had taken oral contraceptives continuously for 7, 10, and 13 yr, respectively. Clinical features and procedures for a correct diagnosis are described. (15 refs)

78-5875 **Pleural Mesothelioma: Clinical and Epidemiological Aspects.** (Fre) Caillard, J. F. (Service de pneumologie, C.H.R. de Lille, Lille, France); Lahoutte, C.; Frimat, P.; Romon, M. *Arch Mal Prof* 38(12): 1040-1047; 1977.

The role of exposure to asbestos fibers in four cases of pleural mesothelioma is discussed. A brief case report is presented for each of the patients (3 men, ages 51, 54, and 39 yr; and 1 woman, age 70 yr), and the diagnostic methods are described. Two of the men, a ship inspector and a ceramics worker, had been occupationally exposed to asbestos. In a retrospective study of 47 patients with mesotheliomas (23 histologically proved, 13 highly probable, and 7 pleurisy cases of probable mesothelioma origin) observed since 1965, exposure to asbestos was definitely established in 5 and considered probable in 13. (no refs)

78-5876 **The Respiratory Epithelium. IV. Histogenesis of Epidermoid Metaplasia and Carcinoma In Situ in the Hamster.** (Eng) Becci, P. J. (Life Sciences Res., IIT Res. Inst., 10 W. 35th St., Chicago, IL, 60616); McDowell, E. M.; Trump, B. F. *J Natl Cancer Inst* 61(2): 577-586; 1978.

The histogenesis of epidermoid metaplasia (EMP) in 108 female Syrian golden hamsters was studied in an attempt to demonstrate direct conversion of mucous cells to epidermoid cells. Seventy-two animals received 15 weekly intratracheal instillations of 3 mg benzo(a)pyrene (BP) + 3 mg ferric oxide in 0.2 ml saline. Trachea and bronchi from four airway levels were studied by light microscopy, histochemistry, and electron microscopy. Within 24 hr of the first instillation, foci of goblet cell hyperplasia and several dividing small mucous granule cells (SMGC) were observed, and some ciliated cells were extruded. Extrusion became widespread at 72 hr, with further increases in goblet cells and SMGC. By 1 wk, the latter were replaced by a layer of nonciliated cuboidal SMGC above a single basal cell layer. One week after the third and fifth instillations, the basal cell layer was covered by two-three layers of metaplastic cuboidal cells that, in turn, were covered by two-three layers of cuboidal and/or flattened surface mucous cells (EMP). These upper two-three layers proved to be SMGC. Extensive keratinization occurred at 10 wk (cornifying EMP). The luminal cornifying epidermoid cells contained PAS-positive, diastase-resistant mucosubstances. Localized areas of marked atypical metaplasia and carcinoma in situ were observed 20-50 wk after the first installation. They were characterized by 1-2 layers of basal ce and 5-10 layers of pleomorphic cuboidal cells. The surfa cells had the characteristics of mucous cells, and cells ne the basal lamina showed features of epidermoid cells. M cous-filled intraepithelial cysts were observed. The resu show that stratification, EMP, and carcinoma in situ c arise from differentiated mucous cells in hamster trache bronchial epithelium, a valid model for studies of human lu carcinoma. (48 refs)

78-5877 **The Respiratory Epithelium. V. Histogenesis Lung Carcinomas in the Human.** (Eng) McD well, E. M. (Dept. Pathology, Univ. Maryland Sch. Medici 31 S. Greene St., Baltimore, MD, 21201); McLaughlin, J. Merenyl, D. K.; Kieffer, R. F.; Harris, C. C.; Trump, B. *J Natl Cancer Inst* 61(2): 587-606; 1978.

Following an analysis of 100 human primary lung ca cinomas, a histogenetic classification of lung carcinom based on cell of origin was proposed, and this classificati was compared with that devised by the World Health Orga zation (WHO). Tumors were grouped under the major hea ings of: tumors from basal and/or mucous cells, tumors fro neurosecretory cells, and tumors from Clara cells. Basal/m cous cell tumors, comprising 88% of this sample, were fu ther classified as epidermoid carcinomas (21%), combin epidermoid and adenocarcinomas (AC, 46%), and A (21%). The criteria for epidermoid differentiation includ the presence of tonofilament bundles, poorly developed end plasmic reticulum (ER) and Golgi apparatus, and well-dev loped desmosomes. The criteria for adeno differentiation i cluded well-developed ER and Golgi apparatus, poor developed desmosomes, extracellular and/or intracellular a veoli, and/or other evidence of cellular secretion such secretory granules. In AC other extracellular alveoli, typic junctional complexes were also present at the luminal aspe where the cell apexes bordered the alveolus. A histogenet classification of lung tumors may be of value in current ar future studies of epidemiologic risk factors, prognosis, pr vention, and treatment of lung cancer. (78 refs)

78-5878 **The Respiratory Epithelium. VI. Histogenes of Lung Tumors Induced by Benzo(a)p rene-Ferric Oxide in the Hamster.** (Eng) Becci, P. J. (Li Sciences Res., IIT Res. Inst., 10 W. 35th St., Chicago, I 60616); McDowell, E. M.; Trump, B. F. *J Natl Cancer In* 61(2): 607-618; 1978.

Lung tumors induced in female golden Syrian hamsters b 15 weekly intratracheal instillations of benzo(a)pyren (BP)-ferric oxide (each, 3 mg) were examined by light an electron microscopy and classified according to a histogenet scheme based on cell of origin. Most of the tumors that resul ed were derived from mucous cells and/or basal cells. Ther were 14 well- or moderately well-differentiated epidermoi

nomas, 6 epidermoid papillomas, and 20 combined epioid and adenocarcinomas. The latter had a wide spec- of epidermoid and adeno components. The epidermoid ponent was characterized in well-differentiated tumors ie presence of intercellular bridges and/or keratinization. -developed desmosomes and numerous tonofilament lles were observed ultrastructurally. The adeno compo- was defined by intracellular and/or extracellular alveoli a well-developed Golgi complex and endoplasmic reticu- and/or evidence of mucous secretion. A tumor com- d of neurosecretory cells that resembled a bronchial car- id in humans was also found. Nests of uniform, small, gonal cells with round-to-oval nuclei were seen light mi- copically, and dense-core secretory granules 1,100-2,200 diameter were present in the cytoplasm. There were also ibrosarcomas that had a very cellular structure, being posed of densely packed ovoid or spindle-shaped cells resembled fibroblasts. The results strongly support the ogenetic classification scheme; ie, a classification based he cell of origin. (39 refs)

5879 **Mechanisms of Late Recurrence after Radical Surgery for Gastric Carcinoma.** (Eng) Iwanaga, (Dept. Surgery, Center for Adult Diseases, Osaka, 1-3 kamichi, Higashinari-ku, Osaka 537, Japan); Koyama, H.; ukawa, H.; Taniguchi, H.; Wada, A.; Tateishi, R. *Am J g* 135(5): 637-640; 1978.

ctors involved in the recurrence of gastric carcinoma were estigated in 25 patients with late recurrence who died 5 or more after surgery and in 129 with early recurrence who d within 2 yr of surgery. The late recurrence rate was high he residual stomach or gastric stump, but the early recur- ce rate was high in the peritoneum and liver. In the late urrence group, the routes of cancer spread were contigu- s invasion and lymphatic spread. In the early recurrence up, dissemination and hematogenous spread were also im- rtant routes. There was a high correlation between both es of recurrence and the following conditions: the amount residual cancer remaining after surgery; the spread of the idual cancer; the rate of cancer proliferation; and host re- tance, as represented by cellular stromal reactions, sinus tiocytosis in lymph nodes, and peripheral lymphocyte unts. The prevention of late recurrence is contingent on the mplete removal of all cancerous tissue combined with adju- nt chemo- or immunotherapy. (12 refs)

-5880 **Polypoid Gastritis. Report of a Case Associated with Gastric Adenocarcinoma and Review of the iterature.** (Eng) Sanner, C. J. (Dept. Internal Medicine, Sec- on Gastroenterology, Univ. Arizona Medical Center, Tuc- n, AZ, 85724); Saltzman, D. A.; Mueller, J. C. *Am J Dig is* 23(5, Suppl): 19s-24s; 1978.

xamination of biopsy specimens from a 46-yr-old man who presented with gastric polyposis revealed chronic superficial gastritis. Directed brushing for cytology and gastric wash cytology revealed no malignant cells. However, follow-up examination 6 mo later revealed not only areas of chronic superficial gastritis, but also adenocarcinoma in an area of erosion. Total gastrectomy was performed; adenocarcinoma was found in 3/5 omental lymph nodes and in one celiac lymph node. Because of the high incidence of gastric carcinoma in patients with atrophic hyperplastic gastritis, a correct diagnosis and long-term follow-up of polypoid gastritis patients are necessary. A review of the literature is presented with emphasis on the association between polypoid gastritis and gastric carcinoma. (43 refs)

78-5881 **Increased In Vitro Tetraploidy: Tissue Specific within the Heritable Colorectal Cancer Syndromes with Polyposis Coli.** (Eng) Danes, B. S. (Lab. Cell Genetics, Dept. Medicine, Cornell Univ. Medical Coll., New York, NY, 10021). *Cancer* 41(6): 2330-2334; 1978.

The occurrence of tetraploidy in cultures established from surgical tissue specimens from patients with familial polyposis coli (FPC) and Gardner's syndrome was studied. The cultures established from all tissue (skin, mesentery, ascending colon, normal mucosa, and colonic wall) obtained from four normal subjects not at risk for either syndrome showed 0%-4% tetraploidy. For the two patients with FPC, 0%-2% tetraploidy was observed in specimens of epidermis, dermis, mesentery, and colonic wall; 12%-20% tetraploidy was observed in samples of normal colonic mucosa; and 18%- 22% tetraploidy was observed in samples of colonic polyps. The occurrence of tetraploidy in the eight patients with Gardner's syndrome was 11%-29% in the epidermis, 0%-3% in the dermis, 0%-1% in the mesentery, 0%-2% in the colonic wall, 14%-26% in the normal colonic mucosa, and 12%-32% in the colonic polyps. The occurrence of tetraploidy in the two patients with a variant form of Gardner's syndrome was 0%-1% in the epidermis; 0%-2% in the dermis, mesentery, and colonic wall; 10%-16% in the normal colonic mucosa; and 15%-20% in the polyps. The results suggest that in Gardner's syndrome and FPC, there is a constant population of tetraploid cells, at least in culture, that may be relevant to the multistep process of carcinogenesis. (12 refs)

78-5882 **Multiple Lymphoid Polyposis and Familial Polyposis of the Colon: A Genetic Relationship.** (Eng) Venkitachalam, P. S. (Dept. Surgery, Jewish Hosp. Brooklyn, 555 Prospect Place, Brooklyn, NY, 11238); Hirsch, E.; Elguezabal, A.; Littman, L. *Dis Colon Rectum* 21(5): 336-341; 1978.

The second literature case of multiple lymphoid polyposis (MLP) of the colon and terminal ileum occurring in a member of a family with a history of congenital familial polyposis (FP) is reported. The grandfather and aunt of the patient, a

12-yr-old boy, had died of carcinoma and polyposis of the colon; his mother had undergone total colectomy and ileostomy for FP. The family history and sigmoidoscopic and x-ray findings strongly suggested a case of congenital FP, and subtotal colectomy was performed without prior biopsy. Microscopically, all lesions examined postoperatively were mucosal lymphoid polyps and not adenomatous polyps. MLP is a disease that occurs in younger patients, who have diffuse involvement of the entire mucosa by small polyps that have a benign course. There is a genetic factor in the etiology of the condition, and a definite link with FP of the colon is found to exist. MLP and congenital FP are accurately distinguishable only by multiple biopsy. Literature cases in which an association between the conditions is mentioned are reviewed. (31 refs)

78-5883 **Pathogenesis of Polyposis of the Large Intestine.** (Rus) Malyshev, Iu. I. (Dept. Oncology, D. I. Ul'ianov Medical Inst., Kuibyshev, USSR); Katorkin, E. N. *Vopr Onkol* 24(4): 35-38; 1978.

In an attempt to evaluate the etiology and pathogenesis of polyposis of the large intestine, various manifestations of the disease were reviewed in 400 patients. The duration of polyposis ranged from 1 mo to 20 yr. Of 62 patients who underwent aspiration biopsy of the small intestine, 28 had clinical symptoms of small intestine involvement and 34 had symptoms of colitis. Villous atrophy of the small intestinal mucosa was detected in 20/62 patients (17 had mild and 3 had marked atrophy). All 180 patients who underwent x-ray examination had symptoms of chronic enteritis. Clinical manifestations of polyposis of the large intestine were correlated with disturbances of absorption in the small intestine. (7 refs)

78-5884 **Colonic Cancer in Inflammatory Bowel Disease (Letter to Editor).** (Eng) Sauer, W. G. (No affiliation given). *Mayo Clin Proc* 53(9): 618; 1978.

The recommendation of prophylactic proctocolectomy for patients with ulcerative colitis, in view of their increased risk of colon cancer with time, is meant only for patients whose ulcerative colitis began in childhood and is of a certain duration and extent, and not for all patients with this disease. (9 refs)

78-5885 **Cytomegalovirus D.N.A. and Adenocarcinoma of the Colon: Evidence for Latent Viral Infection.** (Eng) Huang, E. S. (Dept. Medicine, Univ. North Carolina at Chapel Hill, Chapel Hill, NC); Roche, J. K. *Lancet* 1(8071): 957-960; 1978.

Normal and carcinomatous human colon specimens were examined for the presence of human cytomegalovirus (CM DNA. A total of 28 specimens from 14 patients w analyzed by complementary RNA-DNA hybridization. N patients had adenocarcinoma of the large intestine, 2 h familial polyposis, and 3 had Crohn's disease. Of the se patients with carcinoma of the colon, three were definit positive for CMV DNA (≥2 genome equivalents/cell) a one showed a consistently low level of CMV DNA hybridi tion in the range of 1-2 genome equivalents/cell. None of macroscopically normal tissue (5 cm from tumor) from th patients demonstrate CMV DNA, with the exception of patient who had a recurrence within 2 yr of surgery. C specimen from a patient with familial polyposis had f genome equivalents/cell. Histologically normal and abn mal colon specimens from the two rectal carcinoma patie or from the three patients with Crohn's disease were unifor ly negative for CMV DNA. These findings indicate an sociation between CMV and carcinoma of the colon: hum CMV by itself or with other factors may induce carcino of the colon or human CMV may be prone to multiply become reactivated in carcinomatous and/or associated flammatory cells. (18 refs)

78-5886 **Rat Ileocecal Immunocytoma. An Ultrastr tural Study with Special Attention to the Pr ence of Viral Particles.** (Eng) Burtonboy, G. (Laboratoire Virologie, Faculte de Medecine, Universite Catholique Louvain, 30, Clos Chapelle aux Champs, boite 3055, B 12 Brussels, Belgium); Beckers, A.; Rodhain, J.; Bazin, Lamy, M. E. *J Natl Cancer Inst* 61(2): 477-484; 1978.

Electron microscopic (EM) examination was made of spontaneous sarcomas in Lou/C/Wsl rats. These tum were named ileocecal immunocytomas because of their us site of origin and their capacity to synthesize and secr monoclonal rat immunoglobulins (Ig's). Although necro was prevalent, well-preserved zones were found that consi ed of large, rounded, isolated cells with slightly eccent ovoid nuclei. One or two large nucleoli were often evide and chromatin was condensed in a thin layer along t perinuclear cisterna and around the nucleolus. Large Go complexes and polyribosomes were obvious. The develo ment of the rough endoplasmic reticulum (RER) varied fr cell to cell and was well-developed in only a few cells. In th cells, the RER contained abundant mitochondria. In all t mors examined, small numbers of intracisternal A-type viru like particles were found in the cavities of RER, in smoo vacuoles, or in the perinuclear cisterna. Furthermore, anom lous ribbonlike prolongations consisting of folds of nucle membrane surrounding a leaflet of dense material were fr quently noted. Many cells displayed nuclear degeneratio The sera of 10 tumor-bearing animals had up to 40 mg/ monoclonal Ig, and 2 other rats had Bence Jones protein their urine. It was not possible, however, to distinguish secr tory from nonsecretory tumors by EM. The tumors rese bled plasmacytomas induced in mice and certain human t mors such as Burkitt's lymphoma. (32 refs)

887 **Origin of Intestinal Lymphomas (Letter to Editor).** (Eng) Isaacson, P. (Dept. Pathology, hampton Univ. Medical Sch., Southampton SO9 4XY, and); Wright, D. H. *Lancet* 1(8071): 984-985; 1978.

udy of 66 primary intestinal lymphomas indicated that were of histiocytic origin; no plasma cell tumors were d. This is in contrast to a previous study that claimed 39% of the intestinal lymphomas were plasmacytic in n. Immunoperoxidase studies were performed on 7/23 s of Middle East lymphoma; 6 had the morphological and unohistochemical characteristics of histiocytic lymna. It is suggested that the sequence of progressive hypera and plasma cell proliferation in the gut induces maligcy in the histiocytes of the lamina propria. (10 refs)

5888 **Carcinoma-In-Situ of the Cervix and Vulval Warts Complicating Malignant Lymphoma.** g) El-Maraghy, M. A. (Dept. Midwifery and Gynaecolo-Queen's Univ. Belfast, Belfast, Ireland); Lamki, H.; Pinkn, J. H.; Mawhinney, H. *Ir Med J* 71(5): 159-161; 1978.

3-yr-old woman with malignant lymphoma was treated adiotherapy to the supraclavicular mass of nodes, exci- of the nodes, and chemotherapy with vinblastine, mus-, Natulan, and prednisone. Approx 3 yr later, she was nd to have vulval warts and carcinoma in situ of the cer- Laboratory studies were suggestive of a partial T-cell or -mediated immunity defect in this patient. The imnosuppressive treatment may have made her more susceptible to viral infection. (8 refs)

-5889 **The Morphology of the Earliest Invasive Cell in Low Genital Tract Epidermoid Neoplasia.** g) Genadry, R. (Dept. Gynecology and Obstetrics, Johns pkins Hosp., Baltimore, MD, 21205); Olson, J.; Parmley, Woodruff, J. D. *Obstet Gynecol* 51(6): 718-722; 1978.

e light and electron microscopic characteristics of the dis- ct eosinophilic microinvasive cell in lower genital tract epi- moid neoplasia are described. Ten cases each of grossly asive vulvar, vaginal, and cervical tumors and 12 cases of croinvasive disease (4 vulvar and 8 cervical neoplasms) re examined, and cells at the periphery of 3 vulvar and 3 rvical invasive cancers were subjected to electron microspy. The cells forming the initial protrusion of invasive can- were characterized by large amounts of eosinophilic cytoism, regardless of the degree of differentiation of the rest the tumor. The eosinophilic quality of the invasive cell was sociated at the ultrastructural level with an accumulation contractile protein microfilaments, which apparently presents the basis of the cell's invasive capacity. It is specued that intraepithelial neoplasms that show large, apparly mature cells near the basement membrane should be ewed with more concern than those that demonstrate a full-thickness change of small, dark, basal and parabasal cells without apparent cytoplasmic differentiation. (14 refs)

78-5890 **Electron Microscopic Observations of Vaginal Development in Untreated and Neonatally Estrogenized Balb/c Crgl Mice.** (Eng) Cunha, G. R. (Anatomy Dept., Sch. Medicine, Univ. Colorado, Denver, CO); Lee, A. K.; Lung, B. *Am J Anat* 152(3): 343-381; 1978.

The developing Mullerian vaginae of untreated and neonatally estrogenized [20 μg estradiol (E) given daily for 5 days] 1- to 12-day-old BALB/c Crgl mice were examined by light and electron microscopy. The vaginae of untreated 1-day-old mice had an undifferentiated, pseudostratified columnar epithelium that slowly differentiated into an apparently mucus-secreting epithelium. By day 12, the rough endoplasmic reticulum (RER), Golgi apparatus, and secretion granules were poorly developed features of the apical epithelial cells, but the stromal cells had developed prominent RER and Golgi zones that were involved in the synthesis and secretion of collagen. The collagen accumulated in the intercellular spaces. By day 2, the E-treated mice showed a slight increase in the amount of RER and Golgi structures over untreated controls, and by day 4, there was a significant increase in the number of desmosomes. E accelerated the differentiation of mucus-secreting apical epithelial cells, whose apices became filled with secretory granules, and it promoted the formation of a cornifying epithelium from the underlying basal cells. The latter process was associated with an increase in cellular proliferation and in the number of desmosomes and associated tonofilaments, and with extensive interdigitation of the plasma membranes. In both untreated and E-treated mice, the vaginal epithelium was separated from the stroma by a continuous basal lamina, which suggests that vaginal morphogenesis may be mediated by extracellular materials at the surface between these tissues. (67 refs)

78-5891 **Recurrent Extreme Breast Involution Following Pregnancy and Susceptibility to Breast Cancer: A Hypothesis.** (Eng) Petrakis, N. L. (G. W. Hooper Foundation, Univ. California, San Francisco, CA, 94143). *Med Hypotheses* 4(3): 268-272; 1978.

Nine multiparous Oriental women whose breasts had regressed to a state of flat-chestedness following pregnancy and lactation were found during a breast cancer screening project in the San Francisco Bay Area. During their pregnancies, the breasts of all nine women had developed and enlarged, and five had successfully nursed for ≥2 mo (4 did not attempt to breastfeed). Following cessation of lactation in the women who had breastfed and after delivery in those who had not, the breasts completely regressed to their prepregnant flat-chested state. All of the women had normal menstrual cycles and none suffered from major organic disease. It is

hypothesized that this extreme regression of the breast tissue may represent a marked reduction in genetically determined sensitivity of alveolar and ductal tissue to estrogen and other hormonal factors implicated in the maintenance of breast function during the nonpregnant state. The lower incidence of breast cancer reported in Oriental women may be associated with a relative insensitivity of the breast epithelium to estrogen during the nonpregnant state, which results in a decreased exposure and responsiveness of the breast to secreted exogenous and endogenous carcinogens. (13 refs)

78-5892 **Familial Predisposition to Endometrial Cancer.** (Rus) Shvedova, L.A. (Moldavian Res. Inst. Oncology, Kishinev, USSR). *Akush Ginekol (Mosk)* (6): 58; 1978.

Papillary endometrial carcinoma developed in a 56-yr-old woman whose mother died of cancer and elder sister died of acute leukemia. Of three other sisters, one had papillary endometrial carcinoma; one had uterine fibromyoma, endometrial polyposis, and endocervicosis; and one had uterine fibromyoma with endometrial polyposis. Thus, first-degree relatives of patients with cancer of the corpus uteri constitute a group of increased risk. (1 ref)

78-5893 **Abnormal Chromosomes and Number 1 Heterochromatin Variants Revealed in C-banded Preparations from 13 Bladder Carcinomas.** (Eng) Atkin, N. B. (Dept. Cancer Res., Mount Vernon Hosp., Northwood, Middlesex HA6 2RN, England); Baker, M. C. *Cytobios* 18(70): 101-109; 1978.

Chromosome preparations from 13 patients (11 men, 2 women aged 40-84 yr) with carcinomas of the bladder were subjected to C and G banding and then studied. Six of the patients had received previous surgical treatment for their tumors, but none had received radiotherapy. Variations in the areas of the C bands of the no. 1 chromosomes suggested a constitutional heteromorphism in eight patients; peripheral blood studies in three of the patients confirmed this heteromorphism. Possible pericentric inversions of the heterochromatic regions of the no. 1 chromosomes were present in four patients. Grossly abnormal chromosomes containing major parts of the no. 1 chromosomes were present in seven patients. They included possible isochromosomes for the long arm of no. 1 in two cases and additional C bands on the long arm of no. 1 in two cases. Minute chromosomes that appeared to consist mainly of heterochromatin were present in four patients. (6 refs)

78-5894 **Bladder Carcinoma Associated with Long-Term Treatment with Cyclophosphamide for Multiple Myeloma.** (Ger) Lenzin, A. (Urologische Universitatsklinik, Inselspital, Anna-Seiler-Haus, CH-3008 Bern, Switzerla Cavalli, F.; Sonntag, R.; Zimmermann, A. *Urologe [A]* 1 105-108; 1978.

A 70-yr-old woman with multiple myeloma develop bleeding extended squamous epithelial carcinoma of the nary bladder immediately after treatment with cyclophos mide (total dose 135 g po) for several years. (29 refs)

78-5895 **Chronic Granulocytic Leukemia Following cessful Renal Transplantation.** (Eng) Adle R. (Div. Hematology, Depts. Medicine and Surgery, All Medical Coll., Albany, NY); Lempert, N.; Scharfman, W *Cancer* 41(6): 2206-2208; 1978.

Philadelphia chromosome-positive chronic granulocytic kemia (CGL) occurred in a renal transplant recip (22-yr-old man) on immunosuppressive therapy. At age the patient received and subsequently rejected a sibling ney despite irradiation to the transplant site and treatm with immunosuppressive drugs. Two years later, the was removed and he received a second renal transplant a cadaver donor. The patient achieved normal renal func and was discharged on azathioprine (150 mg/day) and thylprednisolone (12 mg/day). Nine months later, a prog sive thrombocytosis, leukocytosis, and hyperuricemia noted, although the patient remained asymptomatic. was diagnosed, and chromosome studies showed the pres of the Philadelphia chromosome (G22) with translocatio chromosome 7 of the C group. The patient's impaired T function was readily reversed by lowering his dosage of munosuppressive drugs. He was continued on these dr however, and alkylating agents and plateletpheresis used to regulate his peripheral blood count. His CGL been in remission for 10 mo, and normal kidney function been maintained. A review of transplantation centers vealed a total of 5 cases of CGL among a population of 25 renal transplant patients, a fivefold increased incidence the general population. Immunosuppressive drugs shoul used cautiously in nonmalignant disease. (15 refs)

78-5896 **Acute Leukemia after Prolonged Immuno pressive Therapy for Glomerulonephritis.** (E Carcassonne, Y. (Clinique des Maladies du Sang, Univ. M seille, Marseille, France); Gastaut, J. A.; Blanc, A. P. *Ca Treat Rep* 62(7): 1110-1111; 1978.

Two male patients (15 and 56 yr old) developed acute kemia 6 and 4 yr, respectively, after the onset of chloramb therapy for glomerulonephritis. The duration of chemoth py was 3 and 2 yr, respectively, for total doses of 8.9 and g; both patients also received small doses of indometh (1.5 and 3 g). (6 refs)

97 **Busulphan Haemorrhagic Cystitis.** (Eng) Millard, R. J. (Central Middlesex Hosp., London, d). *Br J Urol* 50(3): 210; 1978.

rhagic cystitis developed in a 59-yr-old man who had aking busulfan (total dose, 1.98 kg) since 1973 for c myeloid leukemia. The man had presented with uria of several days' duration and no other symptoms. rities between busulfan and cyclophosphamide, a drug known to cause hemorrhagic cystitis and bladder tuare pointed out. (3 refs)

98 **Stem Cell Leukemia Following Intensive Radiotherapy and Chemotherapy for Hodgkin's se.** (Ger) Trux, F. (Medizinische Klinik, Medizinische emie Erfurt, Nordhauser Strasse 74, DDR-50 Erfurt, rmany); Fink, R.; Wutke, K. *Folia Haematol (Leipz)* : 354-366; 1978.

cell leukemia developed in 2/106 patients treated for kin's disease (HD) during an 8-yr period. A 59-yr-old n with Stage IIIA HD (nodular sclerosis type) responded split-course telecobalt therapy (total dose 4,000 rads to upraclavicular field, 4,400 rads to the mediastinum, rads to a paraaortic abdominal field, and repeated suvicular irradiation with 4,000 rads) and chemotherapy a vinca alkaloid, cyclophosphamide, and prednisolone. ever, the patient developed stem cell leukemia approx after the last irradiation and, despite combination otherapy, died from a cerebral hemorrhage in 20 days. -yr-old man with Stage IIA HD (mixed cell type) red radiotherapy (4,500 rads initially, later 4,300 rads) and otherapy according to a modified version of the De Vita col, in which Mustargen was replaced by cyclophospha- and vincristine by vinblastine. He developed monocytic leukemia and died 5 days after diagnosis. ndifferentiated mesenchymal neoplasm was found at the f an earlier irradiation. Lymphogranulomatosis was not d at autopsy in either patient. (34 refs)

899 **The Blast Crisis of Chronic Granulocytic Leukaemia: Megakaryoblastic Nature of Cells evealed by the Presence of Platelet-Peroxidase--A Cytoical Ultrastructural Study.** (Eng) Breton-Gorius, J. S.E.R.M., U. 91 Hopital Henri Mondor, 94010 Creteil, ce); Reyes, F.; Vernant, J. P.; Tulliez, M.; Dreyfus, B. *Haematol* 39(3): 295-303; 1978.

ytochemical ultrastructural study was made of the akaryoblastic nature of the cells in blast crisis of chronic ulocytic leukemia in a 34-yr-old woman. She had pred, 4 yr earlier, with postpartum hemorrhage, an end spleen, and hepatomegaly. Circulating blast cells were acterized by a high nucleocytoplasmic ratio, dense matin, lack of granules, and a negative peroxidase (PO) reaction on smears. Accordingly, they were termed lymphoid or undifferentiated cells. Most (90%) of these cells could be identified as megakaryoblasts, since they contained PO-like activity in the endoplasmic reticulum (ER) that was distinct from myeloperoxidase. The PO activity had the following similarities to platelet PO: (1) the activity was very sensitive to inhibition by an aldehyde fixative under conditions in which PO activity is preserved in granulocytic precursors: (2) the ER localization was similar to that found in the normal megakaryocytic series; and (3) in the blasts and megathrombocytes, the Golgi apparatus was devoid of activity except for one single cisterna. In addition, this Golgi-associated positive cisterna often exhibited a much higher PO content than the ER cisternae. These data emphasize the possible megakaryoblastic nature of cells in chronic granulocytic leukemia blast crisis. (56 refs)

78-5900 **Diffusion Chamber Culture in Irradiated Rats of Myeloblasts and Promyelocytes from 84 Untreated Patients with Myeloid Leukemias or Refractory Dysmyelopoietic Anemia: Comparison to Continuous Tissue Culture Lines.** (Eng) Greenberger, J. S. (Div. Hematology, Peter Bent Brigham Hosp., Boston, MA); Gans, P. J.; King, V.; Muse, M. B.; Karpas, A.; Moloney, W. C. *In: Advances in Comparative Leukemia Research 1977. Proceedings of the VIIIth International Symposium on Comparative Research on Leukemia and Related Diseases, held in Amsterdam, The Netherlands on 22-26 August, 1977.* Bentvelzen, P.; Hilgers, J.; Yohn, D. S., eds. (New York: Elsevier/North Holland Biomedical Press): 503 pp.; 299-302; 1978.

Bone marrow or buffy coat specimens from 55 untreated patients with myeloid leukemias, 24 with refractory dysmyelopoietic anemia (RDA), and 5 normal subjects were grown in diffusion chambers (DC) implanted into irradiated (750 rads) Sprague-Dawley rats. Fifty-four specimens grew for >21 days: 22/31 acute granulocytic leukemias (AGL), 8/10 chronic myelogenous leukemias in blast crisis, 8/14 chronic myelocytic leukemias, 14/24 RDA's, and 2/5 normal specimens. Immature cells (myeloblasts, promyelocytes, and myelocytes) increased over input numbers in 24 specimens; macrophages increased in 78. Two continuous lines were established from AGL cells explanted from the DC to tissue culture. Twenty other cell lines established directly in vitro showed myeloid cell-associated enzyme increases after butyric acid or DC culture. The DC results indicate that alteration of host environment, as well as intrinsic cellular defects, may regulate the differentiation, proliferation, and malignant transformation of human myeloid cells. (3 refs)

78-5901 **Acute Megakaryocytic Leukemia: Description of a Case Initially Seen as Preleukemia Syndrome.** (Eng) Balducci, L. (Div. Hematology and Oncology, Dept. Medicine, Univ. Mississippi, Jackson, MS); Weitzner,

S.; Beghe, C.; Morrison, F. S. *Arch Intern Med* 138(5): 794-795; 1978.

A 52-yr-old man with sideroblastic anemia that was unresponsive to pyridoxine hydrochloride developed acute megakaryocytic leukemia 3 mo after diagnosis. The leukemia treatment regimen included doxorubicin hydrochloride, cytarabine, vincristine sulfate, and prednisone, but none were effective; he died 1 mo after diagnosis of the leukemia. Autopsy revealed acute megakaryocytic leukemia with involvement of the bone marrow, liver, spleen, adrenals, kidneys, and thyroid. Chromosomal analysis revealed the absence of both diploid and Philadelphia chromosomes. A mode of 45 chromosomes and aneuploidy were present. This is the first known case in which a patient with acute megakaryocytic leukemia had a recognized preleukemia syndrome. (15 refs)

78-5902 **Three Cases of Acute Leukemia in One Pedigree.** (Jpn) Dan, K. (First Dept. Internal Medicine, Tokyo Medical and Dental Univ., Tokyo, Japan); Kuriya, S.; Matsui, Y.; Kudo, H.; Kawada, K.; Nomura, T.; Sano, T. *Jpn J Clin Hematol* 19(6): 844-849; 1978.

Acute leukemia developed in three members of one pedigree over a period of 7 yr, an unusual phenomenon. Case 1, a 59-yr-old man, was diagnosed with acute myeloblastic leukemia (AML) in June 1959. His daughter (Case 2) was hospitalized with complaints of fever, malaise, and petechiae at age 29, and acute lymphoblastic leukemia was diagnosed in January 1976. Investigation of the family history revealed a case of AML (diagnosed in December 1970) in a son of the niece of case 1. There was no evidence of consanguinity in this family. Cases 1 and 2 lived in the same house until the occurrence of leukemia in the former; case 3 lived in a different location. Common environmental factors such as ionizing radiation and toxic chemicals could not be detected among the three cases. The occurrence and significance of familial leukemia in relation to the pathogenesis of leukemia are discussed. (13 refs)

78-5903 **Discordant Chronic Myelocytic Leukemia in Identical Twins (Letter to Editor).** (Eng) Goh, K. (Rochester, NY); Bauman, A. W. *Arch Intern Med* 138(8): 1303; 1978.

The Philadelphia (Ph^1) chromosome could not be demonstrated in two normal subjects whose identical chronic myelocytic leukemia (CML)-diseased twins had typical Ph^1 chromosome. This chromosomal abnormality may be acquired postzygotically, and it may be extended to show no 9q+ or other translocated chromsomes in a normal, identical twin of a CML patient. (5 refs)

78-5904 **Production of Mesenchymal Tumors in Nude Mice by Ph^1 Negative Fibroblasts Obtained from a Ph^1 Positive CML Patient: A Preliminary Re**
(Eng) Wilson, F. D. (Radiobiology Lab., Univ. Califo Davis, CA, 95616); Greenberg, B.; Spangler, W.; Shil M.; Gershwin, M. E.; Dyck, J. *Exp Hematol* 6(6): 549 1978.

The role of hematopoietic stromal elements in the regul of hematopoiesis and in the pathogenesis of myelofibro myeloproliferative disorders was investigated in an ex mental model system permitting the independent stud stromal vs hematopoietic elements in vivo. The mod based on the simultaneous application of three techni (1) growth of bone marrow (BM)-derived fibroblastic nies in vitro; (2) cytogenetic demonstration of m chromosomes associated with hematopoietic malignar and (3) transplantation of isolated stromal elements athymic (nude) mice. Injection of 5-9 x 10^6 Philade chromosomes (Ph^1)-negative fibroblasts from the BM patient with Ph^1-positive chronic myelogenous leuk (CML) produced mesenchymal tumors in 2/5 mice. senchymal tumors were also induced by BM-derived fil lasts from a patient with aplastic anemia who was tr successfully with BM transplantation (2/4 mice) and a normal human (1/2 mice). Morphologic, cytogenetic electron microscopic studies of BM mesenchymal elen in culture and of tumors induced in nude mice by the fibroblasts indicated that the tumor cells were of humar gin and negative for the Ph^1 chromosome. These results tained with the use of human materials, provide the fi vivo morphological and cytogenetic support of the hyp sized relationship of precursors of in vitro fibroblast col to BM stromal elements. (17 refs)

78-5905 **Philadelphia Chromosome-positive Ch Myeloid Leukemia and Polycythemia (Letter to Editor).** (Fre) Pris, J. (Service d'hematologie nique Dieulafoy, CHU Purpan, Place du Dr. Baylac, F 3 Toulouse Cedex, France); Launais, B.; Capdeville, J.; M er, J.; Bourrouilloux, G.; Duchayne, E.; Colombies, P. *Presse Med* 7(13): 1114-1115; 1978.

A 70-yr-old woman developed Philadelphia chromsome-tive chronic myeloid leukemia (CML) 2 yr after an i diagnosis of polycythemia vera. The CML was not attrib to treatment of the polycythemia with ^{32}P because of the dose (7 mCi) involved and the short latent period of the kemia (2 yr). (6 refs)

78-5906 **Trisomy 8 in the Chronic Phase of Philade Negative Chronic Myelocytic Leukaemia.** Lindquist, R. (Section Oncology and Haematology, Medicine, Huddinge Univ. Hosp., S-14186 Huddinge, den); Gahrton, G.; Friberg, K.; Zech, L. *Scand J Hae* 21(2): 109-114; 1978.

case is reported of a 71-year-old woman with Philaia chromosome (Ph^1)-negative chronic myelocytic leua (CML) who possessed trisomy 8 at diagnosis and ughout the chronic stage of her disease. The patient had tory of thyroid gland enlargement and thyroiditis, and 5 cm benign thyroid adenoma was diagnosed on admis-(8/30/74). CML was confirmed at this time but left ued. In 1975, the patient's WBC count increased to 115 /liter, and busulfan treatment was initiated. In Decem-1975, leukemic skin infiltrations appeared; and in July , therapy-resistant blast formation was noted. Chromoes were examined on four occasions, beginning with first ission, and 100% of bone marrow metastases always ved trisomy of chromosome 8. Although trisomy 8 is mon in Ph^1-positive CML in the blast phase, this anomn Ph^1-negative patients is unusual, especially in the early se of the disease. If trisomy 8 can appear at any stage h^1-positive and Ph^1-negative patients, the anomaly would f little prognostic value. (38 refs)

5907 **Down's Syndrome and Leukemia: Mechanism of Additional Chromosomal Abnormalities.** g) Goh, K. (Monroe Community Hosp., Univ. Rochester Medicine and Dentistry, 435 E. Henrietta Road, Roch-r, NY, 14603); Lee, H.; Miller, G. *Am J Ment Defic* 82(6): -548; 1978.

ogenetic findings are reported for five Down's syndrome ents, four with acute leukemia and one with abnormal ulation of granulopoiesis. All patients exhibited marked uploidy and three had morphologically abnormal omosomes. Several metaphases from each patient had omosome abnormalities that suggested a clonal evolution. e frequency of the affected chromosome groups, excluding se characteristic of Down's syndrome, showed that omosome A_1 was involved 9 times; A_2, 6; A_3, 6; C, 105; 14; E, 48; F, 56; G, 56; and abnormal chromosomes, 17. ht G-banding chromosomes had trisomy 21 and/or 22. e abnormal chromosome patterns in these patients could due to nondisjunction in mitosis, an abnormality that re-ed in the phenotypical expression of acute leukemia. (23 s)

5908 **A Near Haploid Clone: 24,XY,t(9;22)(q34;q11) from a Patient in Blast Crisis of Chronic Mye-d Leukaemia.** (Eng) Daniel, A. (Cytogenetics and Cell Bi-gy Unit, Prince of Wales Hosp., Sydney, Australia); Fran-, S. E.; Stewart, L. A.; Barber, S. *Scand J Haematol* 21(2): -103; 1978.

e case of a 58-year-old man with chronic myeloid leukemia o displayed a markedly hypodiploid chromosome complent is reported. Eight days after admission, marrow romosome studies revealed a single clone of ,XY,t(9;22)(q34;q11), indicative of Philadelphia chromosome. Busulfan treatment (2 mg/day) was initiated but discontinued when the patient developed leukopenia. Bone marrow aspirate revealed 98% blasts. The blast cells were very small compared with promyelocytes. The patient died within 2 mo of the removal of a ruptured spleen and the onset of cervical adenopathy. Postmortem marrow chromosome studies revealed a major clone of 24,XY,t(9;22), a minor clone of 46,XY,t(9;22), and possible clones of 47,XY,t(9;22)+del 22(q11), and 48,XY,t(9;22)+C,+de122(q11).There were no clones with a karyotype intermediate between those with 24 and 46 chromosomes. A haploidy event rather than progressive hypodiploid loss may have accounted for the clone with 24 chromosomes. (9 refs)

78-5909 **A Note on Banded Karyotypes in Spontaneous Leukemias of the AKR Mouse.** (Eng) Kodama, Y. (Chromosome Res. Unit, Faculty Science, Hokkaido Univ., Sapporo, Japan); Yoshida, M. C.; Sasaki, M. *Proc Jpn Acad Ser B Phys Biol Sci* 54(5): 222-227; 1978.

Banded karyotypes were analyzed in 20 cases of spontaneous leukemia in AKR mice. The 784 cells examined originated from a thymic tumor in 8 mice, from leukemic spleen in 8, and from both in 4. Cells from metastatic lymph nodes (4 mice) and bone marrow (3 mice) were also examined. Analyses showed that 545 of the cells had 40 chromosomes that were karyotypically normal, 234 had 41 chromosomes, and 5 had 42 chromosomes. The cells with 42 chromosomes were individually trisomic for chromosome 8, 10, 12, 17, and the Y chromosomes, in addition to being trisomic for chromosome 15. Of the total 239 hyperdiploid cells, 220 were trisomic for chromosome 15. Structural abnormalities were rare. Therefore, among 20 cases studied, 12 showed a trisomic 15 cell line coexisting with a karyotypically normal line, although the proportion of the former varied from case to case. These findings agreed with those of earlier studies, except for the rarity of structural abnormalities. The significance of trisomy 15 in the development of leukemia is unknown. (9 refs)

78-5910 **Secondary Malignant Neoplasms in Patients with Hodgkin's Disease.** (Eng) Neufeld, H. (Univ. Manitoba, Winnipeg, Manitoba, Canada); Weinerman, B. H.; Kemel, S. *JAMA* 239(23): 2470-2471; 1978.

A retrospective analysis of 232 cases of Hodgkin's disease (HD) treated at the University of Manitoba between January 1, 1965 and December 31, 1973, revealed secondary malignant neoplasms in five patients. The av follow-up was 44.3 mo. Forty-nine patients had total nodal radiotherapy; 75, upper mantle; 12, inverted Y; 60, both upper mantle and inverted Y at different times in their course; and 34, local radiotherapy alone. A total of 174 patients who received radiotherapy subsequently received chemotherapy with mechlorethamine hydrochloride, vincristine sulfate, procarba-

zine hydrochloride, and prednisone. The five secondary cancers included two cases of acute leukemia (expected incidence was 0.05); both of these patients had received radiotherapy and chemotherapy. The other tumors included one glioblastoma multiforme, one squamous cell carcinoma of the skin, and one prostatic cancer. All neoplasms developed in patients with the mixed cellularity type of HD; this group represented only 28% of all HD cases. Although the therapy may have increased the leukemia incidence in these patients, the frequency was not high enough to abandon combined modality treatment. (11 refs)

78-5911 Systemic Lupus Erythematosus and Lymphoma. (Eng) Green, J. A. (Dept. Medicine and Therapeutics, Univ. Aberdeen, Aberdeen, Scotland); Dawson, A. A.; Walker, W. *Lancet* 2(8093): 753-756; 1978.

Four patients with established systemic lupus erythematosus (SLE) in whom lymphoma subsequently developed are described. All four patients were women ranging in age from 21 to 56 yr at the onset of SLE. Hodgkin's (2 cases) or non-Hodgkin's (2 cases) lymphoma was diagnosed 2 mo to 13 yr after the onset of SLE. An association between the two diseases was previously reported in 14 patients, 6 of whom developed lymphoma either before or at the same time as the autoimmune disease. The 12 patients in whom SLE preceded lymphoma were women with a mean age of 36 yr at the first SLE symptom and a mean age of 46 yr at diagnosis of lymphoma. The common factor underlying the association between the two diseases could be immunodeficiency. The primary lesion in SLE is probably suppressor T-cell dysfunction, which would predispose to abnormal B-cell proliferation in response to an extrinsic antigen or autoantigen. Early biopsy of suspect lymph nodes is recommended for SLE patients. (26 refs)

78-5912 Isolated Hepatic Metastasis from Renal Vein Leiomyosarcoma (Letter to Editor). (Eng) Radhakrishanan, J. (Chicago, IL); Alrenga, D. P.; Ghosh, B. C. *Arch Pathol Lab Med* 102(11): 606; 1978.

An unusual case of liver metastasis from a renal vein leiomyosarcoma occurred in a 93-yr-old woman who had undergone nephrectomy for the primary tumor 5 yr previously. A left hepatic lobectomy was performed; the right lobe was tumor-free. Pathological examination of the resected tissue confirmed the diagnosis of metastatic leiomyosarcoma. (1 ref)

78-5913 Ultrastructural Findings in a Pituitary Tumor Associated with Forbes-Albright Syndrome. (Jpn) Miyagami, M. (Dept. Neurological Surgery, Nihon Univ., Sch. Medicine, Itabashi-ku, Tokyo 173, Jap Nakamura, S.; Moriyasu, N. *Nippon Rinsho Denshi Kenb* 10(3/4): 235-243; 1977.

Several ultrastructural characteristics were studied in a pi tary tumor associated with the Forbes-Albright syndro In the tumor cells, secretory granules with a single lim membrane were markedly irregular in shape and avera 500-800 mμ in diameter. Secretory granules appeared in Golgi zone or near the periphery of the cell. The Golgi c plex was prominent and enlarged, as were the mitochon The rough endoplasmic reticulum was oriented to be lam near the periphery of the cell. There were many processes microvilli on the cell membrane, and myelinlike bodies found in the cytoplasm or intercellular space. (15 refs)

78-5914 Hyperparathyroidism, Chemodectoma, Thy ma, and Myasthenia Gravis. (Eng) Palmer J. (Southern California Permanente Medical Group, Sierra Ave., Fontana, CA, 92335); Sawyers, T. M. *Arch tern Med* 138(9): 1402-1403; 1978.

Two patients with hyperparathyroidism, one (a 52-yr man) with an associated chemodectoma and the othe 57-yr-old man) with an associated thymoma and myasth gravis, are described. These cases may represent an inc plete form of multiple endocrine neoplasia (MEN) syndr type IIa and MEN type I, respectively. (11 refs)

See also:

*(Rev.): 78-5405, 78-5420, 78-5421, 78-5422, 78-5 78-5435, 78-5436, 78-5453, 78-5454, 78-5 78-5456, 78-5457, 78-5458.

*(Chem.): 78-5471, 78-5475, 78-5484, 78-5 78-5486, 78-5488, 78-5489, 78-5 78-5496, 78-5498, 78-5506, 78-5 78-5537, 78-5542, 78-5569, 78-5 78-5581, 78-5583, 78-5584, 78-5 78-5591, 78-5640, 78-5642, 78-5 78-5658, 78-5660, 78-5686, 78-5 78-5688, 78-5689.

*(Phys.): 78-5694, 78-5695, 78-5697, 78-5 78-5711, 78-5714, 78-5717, 78-5 78-5730.

*(Viral): 78-5751, 78-5794, 78-5804, 78-5807, 78-5 78-5851.

*(Immun.): 78-5854, 78-5855, 78-5861.

*(Epid.-Biom.): 78-5918, 78-5925, 78-5927, 78-5 78-5935, 78-5936, 78-5937, 78-5 78-5961, 78-5963, 78-5965, 78-5

5915 **Cancer Epidemiology.** (Spa) Carda Aparici, P. (Instituto Nacional de Oncologia, Ciudad Uni-itaria, Madrid, Spain). *Rev Mex Cir Ginecol Cancer* 5): 140-155; 1977.

cer epidemiology data are presented for Spain. The can-mortality rate was 118/100,000 in 1960 and 143/100,000 973. Men accounted for 52% of the total in 1960 and for % in 1973. In 1960, cancer mortality was highest in north-Spain, lowest in the south. In 1972, mortality was highest ie northeast. In men, stomach cancer mortality accounted 19.2%, lung cancer 18%, prostate cancer 8.7%, liver can-7.2%, laryngeal cancer 5.2%, lymphoma and leukemia %, bladder cancer 4.9%, colon cancer 4.8%, and rectal cer for 2.8% of the total cancer mortality. In women, nach cancer accounted for 17.4%, breast cancer 12%, r cancer 11%, uterine cancer 9.8%, colon cancer 7.9%, phoma and leukemia 5%, lung cancer 4.6%, and rectal cer for 3.2% of the total. (140 refs)

5916 **Cancer Mortality in the State of Sao Paulo, Brazil.** (Por) Pastorelo, E. F. (Departamento de demiologia, Faculdade de Saude Publica da USP, Aveni-Dr. Arnaldo, 715, Sao Paulo, Brazil); Gotlieb, S. L. *Rev ıde Publica* 12(1): 1-15; 1978.

e distribution, during 1970-1972, of cancer mortality ac-ding to the main anatomical sites was determined for the administrative regions of Sao Paulo, Brazil. Cancer mor-ty averaged 8.42% in men and 8.80% in women, and ional differences were a function of industr alization. (9 s)

5917 **Morbidity due to Head and Neck Malignant Tumors in Vinnitsa Oblast, USSR, During 50-1974.** (Rus) Verigina, A. D. (Dept. Hosp. Surgery, edical Inst., Vinnitsa, USSR). *Zh Ushn Nos Gorl Bolezn* 1: 57; 1978.

alysis was made of the incidence of head and neck malig-nt tumors in Vinnitsa Oblast, USSR, between 1960 and 74. Morbidity due to head and neck tumors comprised 3% of the total cancer morbidity. Standardized morbidity lices (per 100,000 individuals) were 22.43 for skin tumors, 5 for cancer of the lip, 1.7 for cancer of the larynx, 0.54 cancer for the tongue and oral mucosa, 0.48 for cancer the jaws, 0.33 for cancer of the pharynx, and 0.27 for ncer of the salivary glands. Morbidity was max in the 50 69 yr age group. Men had a significantly higher incidence lip (20.0 vs 3.27) and laryngeal (4.69 vs 0.13) cancer than omen. (7 refs)

78-5918 **Relative High Frequency of Childhood Hodgkin's Disease in the North of Portugal.** (Eng) Sobrinho-Simoes, M. A. (Laboratorio de Anatomia Patologica, Hospital de S. Joao, Porto, Portugal); Areias, M. A. *Cancer* 42(4): 1952-1956; 1978.

Sex and age factors and the histopathological characteristics of Hodgkin's disease were studied in 322 patients in northern Portugal, particularly the 35 patients <10 yr of age. The male:female ratio in these 35 patients was 2:1. Mixed cellularity was present in 18 patients, nodular sclerosis in 10. The incidence of childhood Hodgkin's disease was 18.2% during 1930-1944, 7.5% during 1945-1959, and 10.8% during 1960-1974. From 1970-1974, however, the frequency decreased to 4.5%. Most children belonged to large families of low socioeconomic status. All but 1/14 patients whose clinical records were reviewed presented with cervical lymphadenopathy as the initial symptom. Nine of these patients had constitutional symptoms at the time of diagnosis, and seven were classified in Stages III and IV. These findings are similar to those previously described in some developing countries of tropical and subtropical regions. (18 refs)

78-5919 **Epidemiology of Lymphogranulomatosis (Hodgkin's Disease). A Review.** (Ger) Berndt, H. (Klinik fur innere Medizin, Bezirkskrankenhaus, Dr.-Wilhelm-Kulz-Strasse, DDR-20 Neubrandenburg, E. Germany). *Arch Geschwulstforsch* 48(5): 435-444; 1978.

Epidemiological data on the occurrence of Hodgkin's disease (HD) in East Germany are presented. The incidence standardized for the European population was 3.2/100,000 in men and 1,8/100,000 in women during 1964-1966, and 3.5/100,000 in men and 2.1/100,000 in women during 1968-1972. The population aged <20 yr accounts for about 10% of the cases. The overall incidence has a first peak of 3.5/100,000 in the age bracket 25-30 yr and a second in the age bracket 65-80 yr. The mortality runs a fairly parallel course. Epidemiological studies have demonstrated familial and space/time clustering, an association with the histocompatibility antigen, and certain occupational factors (increased incidence among woodworkers and persons exposed to benzene), but no influence of ionizing radiation. Primary multiple malignant neoplasms are strikingly frequent in patients with HD, which may also be due to immunosuppressive therapy. HD may not be a nosological entity but rather a clinical and morphological manifestation of two diseases; namely, infectious juvenile granuloma and the true neoplasm in the elderly. (116 refs)

78-5920 **Ethnical and Clinical Aspects of Chronic Lymphocytic Leukemia in Israel. A Survey on 288**

Patients. (Eng) Bartal, A. (Dept. Hematology, Hebrew Univ.-Hadassah Medical Sch., Jerusalem, Israel); Bentwich, Z.; Manny, N.; Izak, G. *Acta Haematol (Basel)* 60(3): 161-171; 1978.

The prevalence of chronic lymphocytic leukemia (CLL) among the large number of ethnic groups in Israel was studied, and clinical findings for each patient were reviewed. The study population consisted of 288 patients (159 men, 129 women) from five medical centers who were diagnosed during 1960-1970. Almost two-thirds of the patients were in their fifth and sixth decades of life at diagnosis. Most (80.5%) of the patients were of East European descent, 14.5% originated from Asia and Africa, and 5% were born in Israel. Furthermore, 63% of all the CLL patients were immigrants from Poland and Rumania. Based on the ethnic distribution of the adult population of Israel during the decade, it is suggested that CLL occurs more frequently in European-born Jews than in Asian and African Jews. Coombs-positive hemolytic anemia was found in only 15/204 patients tested; all but 2 were of East European origin. Estimation of serum immunoglobulin (Ig) levels in 68 patients revealed low IgG levels in 29.4%, low IgA in 61.2%, and low IgM in 51.5%; at least one of these Ig's was below normal range in 74%. The values tended to decrease during the course of the disease. An additional primary malignant tumor was found in 26/206 patients, all of East European origin. Most of these tumors were cancer of the skin and breast. A third malignant neoplasia was diagnosed in 6/26 patients. Hypogammaglobulinemia was more frequent in patients with additional primary malignant tumors and in patients with advanced disease. Possible reasons for the ethnic distribution of CLL in Israel are discussed. (32 refs.)

78-5921 **Leukemia in the Guinea Savanna of Northern Nigeria.** (Eng) Fleming, A. F. (Dept. Hematology, Ahmadu Bello, Zaria, Nigeria). *In: Advances in Comparative Leukemia Research 1977. Proceedings of the VIIIth International Symposium on Comparative Research on Leukemia and Related Diseases, held in Amsterdam, The Netherlands on 22-26 August, 1977.* Bentvelzen, P.; Hilgers, J.; Yohn, D. S., eds. (New York: Elsevier/North Holland Biomedical Press): 503 pp.; 53-54; 1978.

From 1970 to 1976, the following types of leukemia were diagnosed in 136 patients in Zaria and Kaduna, Nigeria: acute (A) lymphatic (21 patients), A myeloid (28), adult chronic (C) myeloid (36), juvenile C myeloid (4), and C lymphatic (47). Men predominated except among rural C lymphatic leukemia patients <45 yr old: depression of cell-mediated immunity during pregnancy may render women in rural Africa susceptible to agents causing this type of leukemia. (6 refs)

78-5922 **Environmental Factors in the Epidemiology of Lymphosarcoma.** (Eng) Goldsmith, J. R. (Epidemiological Studies Lab., California State Dept. Health, Berkeley, CA); Guidotti, T. L. *Pathology Annual* 12(part 411-425; 1977.

Data collected from ongoing studies of the role of envi mental factors in the epidemiology of lymphosarcoma summarized. Geographic mortality analyses suggest that vironmental exposure, including occupational exposure, tributes to the development of lymphosarcoma. Some t of farming and food processing and distribution jobs, and paper work, and electrical work may carry higher normal risks. Proportional mortality studies suggest some building trades and some types of clerical work have an excess risk. Workers in the rubber industry ma at a high risk, but lymphatic and myeloid leukemia had h er mortality ratios. Solvent exposure in rubber workers pears to be related to excess mortality for a variety of phatic tumors. With electrical workers, exposure to solde fumes, actinic radiation and its products, and polychlorin biphenyls (PCBs) used in transformers may play a role in high risk of lymphosarcoma. Similarly, exposure of far to arsenic-containing pesticides may be associated with h er risk. Based on rates for men in large occupational gr that seem unlikely to have specific exposure, it is possibl estimate that approx 33% of cases may have an environm tal exposure. Examination of body burden indices for vents, arsenic, and other metals, and PCBs may facilitate definition of environmental hazards. Compilations of occ tional and exposure histories for cases of lymphosarcom cancer registeries may produce further data on occupati exposures in lymphosarcoma. Social security disability can also be used to observe any trends in incidence. (11 r

78-5923 **Dilemma of Toxic Risks (Letter to Edi** (Eng) Hartford, W. H. (Dept. Chemistry, mont Abbey Coll., Belmont, NC). *Chem Eng News* 56 5; 1978.

A more logical mathematical modeling of the cancer from low concentrations of carcinogens is advocated. C lations of the approx hypothetical probability of canc various doses above background are tabulated accordi four models. (no refs)

78-5924 **Occupational Health and Safety in Metall cal Plants.** (Eng) Taylor, J. C. (Jan H. Rei and Associates Ltd., Oakville, Ontario, Canada). *Healt* 71(794): 141-157; 1978.

The general mechanisms by which ore is processed in m lurgic plants are discussed, and practical solutions to occ tional health hazards associated with these processes are lined. Careful design of the plant can eliminate many of hazards. Technology is available to meet realistic regula to control emissions and provide a safe, healthy environ in these plants. (29 refs)

925 **Incidence and Long Term Survival of Children with Intracranial Tumours Treated in Denmark 1959.** (Eng) Gjerris, F. (Univ. Clinic Neurosurgery, ospitalet, Copenhagen, Denmark); Harmsen, A.; en, L.; Reske-Nielsen, E. *Br J Cancer* 38(3): 442-451;

on tumor incidence and long-term survival of 533 Danildren < 15 yr of age with intracranial tumors diagd during 1935-1959 are presented. The av annual tumor ence was 21/10⁶ children/yr during the 25-yr period. ment consisted of complete macroscopic surgical reil in 35% of the cases, partial removal or, more infretly, biopsy in 50%, and radiotherapy (usually postoperar) in 36%. In 75% of the children receiving therapy, the skin doses were between 2,500 and 6,000 Operative mortality was 28% during the 25-yr period. e 345 children who survived > 1 mo after surgery, 119) were alive in 1974. Thirty-five percent of children surg > 1 mo with supratentorial midline astrocytomas and of those with hemispheral astrocytomas had a 25-yr val. Only 5/19 children with a supratentorial epenoma survived > 20 yr. The long-term prognosis was poor children with craniopharyngiomas, with many recures developing after 10 yr. Among children with infratenl tumors, only those with cerebellar astrocytomas had gh long-term survival rate. Children with brain stem tus, ependymomas, or medulloblastomas had a poor progs. There were no significant differences in long-term surl between patients with supratentorial vs infratentorial ors or between children with midline vs lateral supratenl tumors. The histological diagnoses in survivors who received radiotherapy were so heterogeneous that it was ossible to evaluate the influence of treatment on the -term prognosis. (40 refs)

926 **The Epidemiology of Intracranial Meningiomas in Women in Los Angeles County.** (Eng) Pres-Martin, S. (Univ. California, Los Angeles, CA). *Diss r Int B* 39(5): 2238-2239; 1978. (no refs)

927 **Aetiological Factors in Brain Tumours (Meeting Abstract).** (Eng) Stortebecker, P. (Stockn, Sweden). *Acta Neurochir (Wien)* 42(3/4): 252; 1978. efs)

928 **Cancer Epidemiology. Part IV: Lung Cancer.** (Eng) Harberg, J. (Wisconsin Clinical Cancer ter, 1900 University Ave., Madison, WI, 53705); Bucha-Davidson, D. J. *Wis Med J* 77(9): 18; 1978.

k factors for lung cancer (including socioeconomic up; cigarette smoking; certain occupations; and exposure to asbestos, uranium, chromates, or radiation) are surveyed briefly. (12 refs)

78-5929 **Occurrence of Lung Cancer at a Special Steel Manufacturing Plant.** (Swe) Rottner, B. (Fagersta AB, Fagersta, Sweden). *Lakartidningen* 75(20): 2022-2023; 1978.

Lung cancer mortality among employees of Fagersta AB, a manufacturer of special high-chromium steel, during 1956-1976 was determined in a case-control study. Metallic and trivalent chromium occurs in various technological processes. The overall mortality in the town of Fagersta over the 10-yr period was 3,112, but there were only 23 deaths from lung cancer. Compared with the national av, lung cancer mortality is underrepresented in Fagersta, which may be due to the small number of inhabitants. Twelve of the 23 lung cancer patients had been employed by Fagersta AB; 6 were office workers. Twenty-two of the 42 controls had been employed by the steel plant. The findings show no influence of employment at the chromium steel plant on lung cancer mortality. (7 refs)

78-5930 **Incidence of Cancer in Patients with Active Pulmonary Tuberculosis.** (Jpn) Fukutome, T. (Fukuoka-Higashi Natl. Hosp., Koga-Cho, Fukuoka-ken, Japan). *Fukuoka Igaku Zasshi* 69(3): 98-102; 1978.

Cancer incidence in 1,358 pulmonary tuberculosis patients treated at a Fukuoka, Japan, hospital from January 1971 to April 1977 was evaluated by the person-year method. The incidence was 6.0 vs an expected incidence of 6.74. This difference was not statistically significant. In 13/14 patients, the interval between the diagnosis of pulmonary tuberculosis and cancer appearance was > 5 yr. Apparently, tuberculosis lasting > 5 yr has no suppressive effect on cancer development. (16 refs)

78-5931 **Lung Cancer in Workers in a Nickel Refinery.** (Eng) Kreyberg, L. (Inst. Pathology, Univ. Oslo, Oslo, Norway). *Br J Ind Med* 35(2): 109-116; 1978.

The occurrence of lung cancer among nickel workers was studied based on 44 cases of lung cancer in persons employed in a nickel refinery during 1927-1974. Among those who began their employment between 1927 and 1939 (Series I), 5 developed cancer after 17-22 yr and 13 developed cancer after 31-40 yr. The cases with the longest development time had the lowest exposure to nickel. Among those who began their employment after 1945 (Series II), 17 developed tumors after 4-19 yr and 7 developed cancer after 20-25 yr. At diagnosis, the mean age of the series I and II workers was 57.6 and 56.0 yr, respectively. Among the 32 subjects with Group I tumors

(epidermoid and small cell anaplastic carcinoma), 29 were smokers; among the 7 subjects with Group II tumors (adenocarcinomas and other histological types), only 3 were smokers. These data suggest that tobacco smoking is an important additional factor in lung cancer in nickel workers. Among the employees not exposed to nickel, there was one with a Group I tumor and one with a Group II tumor. This study suggests that the risk of lung cancer may be higher in nickel workers than in the general population. (13 refs)

78-5932 **Air Pollution and Cancer in Houston, Texas: A Causal Relationship?** (Eng) Marmor, M. (Inst. Environmental Medicine, New York Univ. Medical Center, 550 First Ave., New York, NY, 10016). *J Am Med Wom Assoc* 33(6): 275-277; 1978.

Respiratory cancer mortality rates from a previous study of cancer mortality and air pollution in Houston, Texas, were recast to allow investigation of possible confounding due to socioeconomic status and occupation. Cross tabulation of white male respiratory cancer mortality rates by air pollution categories and income levels for 1965-1969 yielded data that were consistent with a very strong health effect of air pollution. However, a similar recasting of the female mortality rates revealed a lack of association between air pollution levels and mortality rates. A synergistic effect between occupational and residential air pollution exposures could explain the association in men and the lack of an association in women. The possibility that geographic smoking patterns may have created a spurious relationship between air pollution and respiratory cancer cannot be eliminated. Selective migration and current air pollution patterns (compared with those of 20 yr ago) may also be confounding variables. In conclusion, it is difficult to argue that air pollution is responsible for the patterns of respiratory cancer mortality in Houston or any other city. (5 refs)

78-5933 **Identification of Lung Cancer Risk Groups by Directed Mass Screening.** (Hun) Abraham, E. (Tudogondozo Intezet, Fovarosi Bajcsy-Zsilinszky Korhaz-Rendelointezet, Budapest, Hungary). *Orv Hetil* 119(17): 1033-1036; 1978.

The results of a 1975 mass screening of 10,339 men and 10,089 women for lung tumors are presented. The mass screening was complemented by a computer-evaluated questionnaire on risk factors (age > 40 yr, smoking habit, occupational and other exposure, radiological change on previous chest x-rays, 2 or more respiratory complaints, and major surgery within the last 3 yr). During the first 1.5 yr following the mass screening, 78 cases of lung cancer were detected in the screened population (64 in men, 14 in women; incidence 619/100,000 in men, 107/100,000 in women). Among men, the incidence was 405/100,000 for those with negative previous chest x-rays, 1,069/100,000 for those with minor radiological changes, and 915/100,000 for those with major x-r changes. The corresponding incidences in women w 54/100,000, 157/100,000, and 403/100,000. In the risk gro (changes on previous x-rays, smoked > 100,000 cigarette incidence was 1,342/100,000 in men and 985/100,0 in women. Additional harmful occupational expos caused the incidences to be 1,105/100,000 in men a 1,093/100,000 in women. In the no-risk group (ne tive previous x-ray, work in unpolluted air), the lu cancer incidence was 0/1,124 in men and 1/5,129 women. The findings indicate that the difference lung cancer incidence between men and women is d to differences in smoking habits and occupational exp sure; 10% of the men and 40% of the women screened w in the no-risk group. (13 refs)

78-5934 **Occupational Distribution of Patients w Lung Cancer and Those with Chronic Bronch Obstruction, Bronchial Asthma, and Sarcoidosis in Be Switzerland.** (Ger) Scherrer, M. (Pneumologische Abteilu Medizinische Universitatsklink, Inselspital, CH-3010 Be Switzerland); Zeller, C.; Zweifel, J. *Schweiz Med Wochens* 107(46): 1656-1661; 1978.

The occupational distribution of 553 patients with lung ca cer, 233 with chronic bronchial obstruction, 1,397 with bro chial asthma, and 217 with sarcoidosis was studied with spect to smoking habits, degree of physical labor, a occupational and climatic exposures. Statistical analy showed a definite prevalence of subjects who worked indo among patients with sarcoidosis and bronchial asthma, gardless of smoking habits. In contrast, chronic obstruct lung disease and, especially, lung cancer seemed to oc predominantly in subjects whose jobs involved hard physi labor and heavy inhalative and climatic influences, regardl of smoking habits. Indoor workers tended to be spared lung cancer, as were workers in the metals, synthetics, a chemical industries. An increased incidence of lung can was seen among outdoor workers, such as construction a farm workers, who are exposed to exhaust gases and cigare and cigar smoke while performing hard physical labor. cause of continuous physical exertion, their breathing is de and frequent, and the effect of hazardous air pollution m thus be considerably increased. (24 refs)

78-5935 **Pneumoconiosis and Lung Cancer Japan--Statistical Analysis of 1,172 Autopsi Cases During 1958-1974.** (Jpn) Suzuki, T. (Dept. Patholo Sapporo Medical Coll., Sapporo-shi, Hokkaido 060, Japa Kikuchi, I.; Okuda, M. *Jpn J Cancer Clin* 24(3): 179-1 1978.

Cases of pneumoconiosis recorded in the Annual of Pathol ical Autopsy Cases in Japan during 1958-1974 (Group were reviewed and compared with those occurring in patie autopsied at Iwamisawa Rosai Hospital during 1956-19 (Group 2). Most of the silicotic patients on the island of H

in Northern Japan were treated at this hospital where st all death cases are autopsied. Lung cancer was d in 179/1,172 Group 1 patients and in 49/327 p 2 patients. The incidences of lung cancer in groups were significantly higher than that in all > 35 yr old autopsied in Japan during 1917- and the lung cancer mortality rate was higher the rate for all men > 35 yr old during 1967-1971. noteworthy that the incidence of lung cancer in Groups d 2 was almost identical (15.3%, 15.0%). The results est that there is a significant correlation between moconiosis and lung cancer. (19 refs)

936 **Epidemiologic Study of Precancer and Cancer of the Larynx.** (Bul) Dukhlev, S. (Regional Oncological Dispensary, Stara Zagora, Bulgaria). *Onkologiia*): 8-12; 1978.

factors were evaluated in 234 patients with cancer of the nx, 240 patients with precancer of the larynx, and 743 thy controls. Residence in urban areas, smoking, alcohol umption, and occupational exposure to various environtal pollutants increased the risk of cancer of the larynx. refs)

5937 **Cancer of the Larynx and Environmental Factors.** (Rus) Mgaloblishvili, G. N. (Dept. Otorlaryngology, Res. Inst. Oncology, Tbilisi, USSR); ordzhadze, N. A.; Gogeliani, G. K.; Gobronidze, I. A.; lidze, D. V.; Ivanidze, T. G. *Vopr Onkol* 24(5): 66-69; .

incidence of laryngeal carcinoma in the Georgian Republ f the USSR is discussed. Between 1971 and 1975, cancer ne larynx was diagnosed in 572 patients ($2.4/10^6$). The up included 535 men and 37 women (420 men and 26 nen were in the 40- to 69-yr-old age group). There were patients with Stage I, 121 with Stage II, 405 with Stage and 23 with Stage IV cancer. Histologically, most of the ents had squamous cell carcinoma. When these patients e compared with 169 matched healthy controls, it was nd that the patients consumed more hot food, onions, garand alcohol and they had greater exposure to various nicals, dust, and smoke. (12 refs)

5938 **Liver Cirrhosis, Tobacco, Alcohol, and Cancer among Blacks.** (Eng) Keller, A. Z. (Epidemigic Res., Dept. Medicine, and Surgery, Veterans Ad.-151 G, 941 N. Capital St., NE, Room 6303, Washing. DC, 20431). *J Natl Med Assoc* 70(8): 575-580; 1978.

bacco use, alcohol consumption, and age were character- in relation to distribution of cancers by anatomical site ong male black cancer patients with (n = 32) and without = 73) cirrhosis. Noncirrhotic (NC) black and white male cancer patients were also characterized with respect to these variables. All patients in the series were discharged from US veterans hospitals. Among the black patients, the mean age of the cirrhotics (C's) was significantly lower than that of the NC's. Esophageal cancer was more than three times as frequent but stomach cancer was only one-fourth as frequent in the latter. However, only the excess of liver and gallbladder cancer (42.83% vs 1.50%) and lack of prostatic (26.2% vs 22.10%) and pulmonary cancer (8.31% vs 32.28%) within the C group were statistically significant. Smoking patterns between the two groups were not significantly different, but only one-fifth as many C patients were nonsmokers, and notably more C's smoked ≥ 20 cigarettes/day (75% vs 59.1%). C's drank whiskey as well as other alcoholic beverages significantly more often than NC's and there was a significant deficit of nondrinkers and an excess of heavy drinkers in this group. In a comparison of the 73 black NC's with 374 white NC cancer patients, ratios of liver, stomach, and prostate cancer were more than twice as high for blacks. However, esophageal cancer occurred at a similar frequency in both groups. Significantly more black patients smoked < 20 cigarettes/day (23.9% vs 9.5%), and significantly more white patients smoked < 20 cigarettes/day (74.8% vs 60.6%). Although blacks and whites exhibited similar profiles of drinking behavior by quantity, whiskey drinkers were significantly more numerous among the blacks. Thus, factors associated with smoking and drinking (especially whiskey), if not these habits themselves, are probably related to the increased risks of blacks for stomach and liver cancer compared with NC whites and for esophageal and hepatic cancer compared with NC blacks. (18 refs)

78-5939 **Increases in Laryngeal Cancer in Britain and Australia in Relation to Alcohol and Tobacco Consumption Trends.** (Eng) McMichael, A. J. (Div. Human Nutrition, Commonwealth Scientific and Industrial Res. Organisation, Kintore Ave., Adelaide, S. Australia 5000). *Lancet* 1(8076): 1244-1246; 1978.

The recent increase in the incidence of esophageal and laryngeal cancer in Britain and Australia, particularly in younger women, is examined. The time trends in sex-specific mortality from cancers of the larynx and esophagus throughout this century, in both Britain and Australia, show strong correlations with alcohol consumption. Since World War II, per capita alcohol consumption has almost tripled in Australia and it has increased by 70% in Britain. The time trends in relative cancer mortality between the two countries follow the trend in relative alcohol consumption quite closely, with a lag of 15 yr. The recent greater percentage increase in laryngeal cancer risk in British women than men, especially for younger women, is consistent with a joint effect of alcohol and tobacco. In women, consumption of both alcohol and cigarettes has increased in the past 30 yr, whereas the consumption of cigarettes by men has not. These results provide evidence for the close relationship between alcohol consumption and cancer of the larynx. (25 refs)

78-5940 **The Carcinoembryonic Antigen (CEA) in Urban Populations: Epidemiological Studies.** (Ger) Schlipkoter, H. W. (Medizinische Institut fur Lufthygiene und Silikoseforschung, Gurlittstrasse 53, D-4000 Dusseldorf, W. Germany); Baginski, B.; Kramer, U. *Zentralbl Bakteriol (Orig B)* 166(2/3): 136-143; 1978.

Serum carcinoembryonic antigen (CEA) levels were measured during 1975-1976 in 50-yr-old men living in various areas of North Rhine-Westphalia, West Germany. High CEA levels were correlated with the number of cigarettes smoked and with chronic bronchitis (CB); even nonsmokers with CB had significantly higher levels than those without the disease. There was also a positive correlation between CEA levels and length of residence (>5 yr) in an industrialized city such as Duisburg, but not in a rural town such as Gummersbach. Repeated determinations in over the 2 yr showed that the high CEA values of smokers remained stable. A graphical representation of CEA values in Cologne resident demonstrated that levels were higher in those living in industrial areas than in those living in nonindustrial areas of the city. The feasibility of using only nonsmokers to evaluate the effect of air pollution on CEA levels is discussed. (9 refs)

78-5941 **Preliminary Study of the Mortality due to Malignant Gastrointestinal Tumors in Different Districts of Krakow, Poland, in Relation to Dietary Habits.** (Pol) Jedrychowski, W. (Zaklad Epidemiologii, Instytut Medycyny Spolecznej AM, Kopernika 7, 31-501 Krakow, Poland); Popiela, T.; Elgiet, W.; Cholewka, K. *Pol Tyg Lek* 33(18): 725-729; 1978.

A preliminary study was made of the 1974 mortality due to gastrointestinal neoplasms in four different districts of Krakow, Poland, and its possible relationship to dietary habits. The standardized mortality rates (SMR) for all cancers were 131.1 (144.2 for men and 199.1 for women) in Krowodrza (1); 139.9 (159.1 for men and 122.4 for women) in Nowa Huta (2); 141.2 (154 for men and 129.6 for women) in Podgorze (3) and 202.7 (201.6 for men and 203.8 for women) in the center city (4). The corresponding SMR for gastrointestinal tumors were 60.7 (65.6 for men and 56.3 for women) in district 1, 74.8 (83 for men and 67.4 for women) in district 2, 52.5 (47.7 for men and 56.9 for women) in district 3, and 94.7 (108.1 for men and 82.4 for women) in district 4. Analysis of the types of food consumed showed that the differences in overall cancer mortality and in gastrointestinal cancer mortality cannot be explained unequivocally by dietary habits. The higher cancer mortality in the center city may be due to higher air pollution levels. (14 refs)

78-5942 **Epidemiology of Gastric Adenocarcinomas.** (Fre) Audigier, J. C. (C.N.R.S. Laboratoire 005440, pavillon H, hopital Edouard-Herriot, 1, avenue Rockefeller, 69374 Lyon Cedex 2, France); Lambert, R. *Rev Prat* 28(45): 3409-3417; 1978.

The risk of gastric cancer is higher in the elderly, in men, subjects with blood group A, and in subjects of the lov socioeconomic classes. The incidence is distributed unever among various countries and within the same country a evenly in rural and urban areas. Dietary factors probably p a major role in the etiology of this cancer. (11 refs)

78-5943 **Talc-coated Rice as a Risk Factor for Stoma Cancer.** (Eng) Stemmermann, G. N. (Kuak Medical Center, 347 N. Kuakini St., Honolulu, HI, 9681 Kolonel, L. N. *Am J Clin Nutr* 31(11): 2017-2019; 1978

The hypothesis that talc-coated rice (TCR) increases the r of stomach cancer was tested by comparing the cancer in dence rates of indigenous Japanese, who do not consu TRC and Hawaiian-Japanese, who consume TCR almost clusively. The results show that the Japanese in Japan h very high rates of stomach cancer but the Hawaiian-Japan have intermediate rates. The additional finding that Filipi in Hawaii have very low gastric cancer rates yet consume greatest amounts of TCR convincingly demonstrated t there is no correlation between frequency of exposure to T and gastric cancer incidence. (14 refs)

78-5944 **Precancerous Lesions of the Stomach in Co Rica.** (Spa) Salas, J. (Servicio de Patologia, H pital San Juan de Dios, San Jose, Costa Rica). *Patol (Mex)* 15(2): 63-79; 1977.

Lesions of the gastric mucosa were studied in 500 stoma from 500 consecutive autopsies performed on subjects b in different provinces of Costa Rica. The patients inclu 254 males and 246 females aged 0-45+ yr. Intestinal m plasia of the gastric mucosa was found in 247 patients (males and 117 females). The frequency of intestinal m plasia was 9/91 in patients aged 0-14 yr, 21/54 in those a 15-29 yr, 33/64 in those aged 30-44 yr, and 184/291 in th aged $\geq$45 yr. The frequency was higher in subjects born high gastric cancer risk areas (central valley: 137/249) those born in low gastric cancer risk areas (major cities, l lands and coastal areas: 91/225), and it remained unchan for subjects who were born in high-risk areas and then mo to low-risk areas. Localities with a higher prevalence of m plasia showed a higher incidence of gastric cancer as w Since intestinal type gastric cancer is predominant in C Rica, these findings support the hypothesis that intest metaplasia of the gastric mucosa is a precancerous lesion. refs)

78-5945 **Breast Cancer and Diet among the Japanes Hawaii.** (Eng) Nomura, A. (Japan-Hawaii C cer Study, 347 N. Kuakini St., Honolulu, HI, 96817); H derson, B. E.; Lee, J. *Am J Clin Nutr* 31(11): 2020-2025; 19

evaluate the hypothesis that breast cancer may be as-
ated with the intake of dietary fat, cholesterol, and animal
ein, the dietary history of 86 Hawaiian-Japanese men
se wives had breast cancer was compared with that of
0 Japanese men whose wives did not have the disease.
to the lack of a standarized method of dietary data col-
ion, three different techniques were employed: (1)
prehensive 24-hr dietary recall, (2) weekly food frequen-
urvey, and (3) an estimate of the weekly quantitative con-
ption of various food items. The results were consistent
one method to another and indicated that, although the
groups did not differ significantly in daily nutrient in-
, breast cancer spouses consumed more American foods
have a high fat or protein content, such as beef, butter,
garine, cheese, corn, and wieners. In contrast, the control
up consumed more Japanese items, such as green tea,
anese soups, nori, and other seaweeds. It is concluded that
her study of the American diet may be vital in relating
ritional factors to breast cancer. (16 refs)

5946 **Epidemiology of Breast Cancer with Special Reference to the Role of Diet.** (Eng) Hirayama, (Epidemiology Div., Natl. Cancer Center Res. Inst., kiji 5-Chome, Chuo-ku, Tokyo, Japan). *Prev Med* 7(2): -195; 1978.

e low incidence of breast cancer in Japan, the recent in-
ase of this disease (especially in women aged 45-59 yr), and
role of dietary fat intake and body size in these develop-
nts are discussed. Epidemiological studies of 142,857
men aged >40 yr indicated that the risk was 8.5 times
her in women of high socioeconomic strata who eat meat
ly than in women of low socioeconomic strata who do not
meat daily. A high positive correlation was noted between
capita fat intake and adjusted breast cancer death rates
different districts of Japan. It was estimated that the breast
cer death rate will rise to the US level when Japanese
tary fat intake approaches current US levels. The close
relation with fat intake resulted mainly from the con-
nption of pork and animal fat. The recent increase in
ast cancer death rates was also found to be under the
nbined influence of the daily intake of animal fat and
2-furyl)-3-(5-nitro-2-furyl)acrylamide, a highly mutagenic
d additive widely used in Japan from 1965 to 1975 and
own to produce mammary carcinoma in rats. A series of
e-control studies revealed an increased risk of breast can-
with increasing body size, especially in postmenopausal
men. The recent breast cancer increase could therefore be
eflection of the fact that Japanese women are becoming
avier, especially after age 30. (13 refs)

-5947 **Barrier Contraceptive Practice and Male Infertility as Related Factors to Breast Cancer in arried Women. Preliminary Results.** (Eng) Gjorgov, A. N. ept. Obstetrics and Gynecology, Hosp. Univ. Pennsylnia, 3400 Spruce St., Philadelphia, PA, 19104). *Oncology* (3): 97-100; 1978.

A case control study was conducted to test the hypothesis that a reduced exposure to human seminal factors in the early reproductive life of women is a risk factor in breast cancer. A total of 153 consecutive breast cancer patients, aged 35-60 yr, were matched by age, social status, and method of contraceptive practice with 168 controls. The relative risk of exposure to the hypothetical semen-factor deficiency was 4.7 times greater for the breast cancer patients than for the controls. When male infertility factors were excluded from the analysis, the risk of breast cancer in the same population in the US was estimated as five times greater for women who use barrier contraceptive methods (condom and other) than for women who use nonbarrier methods (diaphragm and other). The reduction in breast cancer incidence by eliminating the barrier contraceptive techniques would be not < 50% in married white women. (36 refs)

78-5948 **Significance of Hysterectomy in the Genesis of Breast Tumors.** (Rus) Ismailov, A. Kh. (Medical Inst., Blagoveshchensk, USSR); Kositsyna, M. V.; Pal'chik, E. A. *Akush Ginekol (Mosk)* (6): 56; 1978.

Of 232 women who underwent hysterectomy for uterine fibromyoma, 18.4% developed mastopathy within 5 yr of surgery and 37.9% developed mastopathy within 10 yr of surgery. (2 refs)

78-5949 **Menstrual Cycle Patterns and Breast Cancer Risk Factors.** (Eng) Wallace, R. B. (Dept. Preventive Medicine, Univ. Iowa, Iowa City, IA, 52242); Sherman, B. M.; Bean, J. A.; Leeper, J. P.; Treloar, A. E. *Cancer Res* 38(11, part 2): 4021-4024; 1978.

The relationship between abnormal menstrual cycle patterns and age at menarche, menopause, and first parity, three variables related to breast cancer incidence, was examined using a data set of women who, beginning in 1934, recorded menstrual, contraceptive, reproductive, and related medical events through life. Many daughters of the original subjects were also enrolled and, to date, nearly 5,000 women have participated. The results include data collected through 1975. Subjects taking oral contraceptives or with any gynecological surgery that might interfere with cycle patterns were excluded. Women with late onset of menarche had longer and more variable cycles in the 10 yr after menarche than those with early onset. Cumulative fertility in women after marriage did not differ according to cycle length and variance. Late menopause may be a breast cancer risk factor because of relative estrogen excess and progesterone lack, as reflected in longer, more varied cycle patterns. Late menopausal age is also a risk factor for endometrial cancer, which may also be related to persistent estrogen stimulation. In this analysis, only simple measures of cycle patterns, means, and variance were examined. A single or small number of episodes of prolonged amenorrhea may possibly be of more pathophysiological importance than deviations from av cycle length of, for example, 1 wk. (12 refs)

78-5950 **Dormancy and Spontaneous Recurrence of Human Breast Cancer In Vitro.** (Eng) Yuhas, J. M. (Cancer Res. and Treatment Center, Univ. New Mexico, 900 Camino de Salud, N.E., Albuquerque, NM, 87131); Tarleton, A. E. *Cancer Res* 38(11, part 1): 3584-3589; 1978.

The hypothesis that hormone-dependent tumor cells survive endocrine therapy in a viable but nongrowing state, adapt to the absence of hormones genetically or physiologically, and then resume growth was demonstrated in vitro using a cell line derived from a brain metastasis of a human mammary adenocarcinoma (MDA-361). The responses of monolayers and multiple tumor spheroids (MTS's) of the MDA-361 line were compared in two types of media: one in which exogenous insulin (I: 10 μg/ml) had been added (I+) and one in which the only I present was that remaining after dialysis (I-). The monolayer cultures required I for growth and for maintenance of viability, as evidenced by the rapid and complete degeneration of the cells after they were transferred to the I- medium. Detachment occurred within 24-48 hr, and the few cells that remained attached (<0.1%) doubled every 3-4 wk. Upon transfer to I- medium, the MTS's became less dependent on and more responsive to this hormone and, after a dormant period of approx 6 wk, eventually resumed growth. During culture in I- medium, the MTS's appeared normal but reduced in size (max of 12%-40% loss of volume). The spontaneous regrowth in the absence of I continued at least through 3 mo. In terms of overall kinetics, the MTS's paralleled the behavior of residual tumors in vivo. In both cases, progressive tumor growth occurs in the presence of a specific growth factor (ie, I), shrinkage occurs upon its removal, stability persists for a prolonged period, and then growth resumes. (22 refs)

78-5951 **Reproductive Factors and Risk for Breast Cancer in Iceland.** (Eng) Tulinius, H. (Icelandic Cancer Registry, P.O. Box 523, 101, Reykjavik, Iceland); Day, N. E.; Johannesson, G.; Bjarnason, O.; Gonzales, M. *Int J Cancer* 21(6): 724-730; 1978.

The risk of breast cancer was compared with various aspects of a woman's reproductive history in a prospective study of 31,453 Icelandic women born between 1906 and 1945. Among these subjects, 216 had developed breast cancer by 1975. Age at menarche had a slight influence on breast cancer risk (increased risk associated with earlier menarche), and this influence remained after further adjustment for parity and age at first pregnancy. Risk also increased with increasing age at first pregnancy and with nulliparity. The risk decreased with larger number of children, the effect being independent of age at first pregnancy. It is suggested that, given the linearity of increase in breast cancer risk with interval to first pregnancy, before a woman becomes pregnant her breast tissue is in a condition particularly susceptible to the action of some carcinogenic influence. Further, the mechanism of action of this putative carcinogenic influence appears to be different from the mechanism mediating the increased ceptibility among certain populations. (24 refs)

78-5952 **The Epidemiology of Epithelial Ovarian Ca in Women Aged 25-49.** (Eng) Casagrande, (Univ. California, Los Angeles, CA). *Diss Abstr Int B* 3 2235-2236; 1978. (no refs)

78-5953 **Epidemiological Study of Endometrial Ca** (Jpn) Masubuchi, K. (Dept. Gynecology, cer Inst. Hosp., Toshima-ku, Tokyo 170, Japan); Nemot *Gan No Rinsho* 24(8): 766-771; 1978.

Examination of 197 endometrial cancer patients at the cer Institute Hospital, Tokyo, Japan, during 1970-197 vealed that women at high risk for endometrial cancer those >50 yr of age (3.4% were <39 yr old), nullipa having a max blood pressure >160 mm Hg, weighing kg (7.3% weighed <39 kg), and complaining of genital b ing. The diagnostic accuracy was 81.2% using endom aspiration cytology. Among 13 cases diagnosed as noncar ous at first biopsy, 8 were suspected of being malignan aspiration cytology. (23 refs)

78-5954 **Mortality of Female Workers in a Rul Manufacturing Plant.** (Eng) Andjelkovich (Occupational Health Studies Group, Sch. Public He Dept. Epidemiology, Univ. North Carolina, Chapel Hill, 27514); Taulbee, J.; Blum, S. *J Occup Med* 20(6): 409- 1978.

The 10-yr mortality experience of a cohort of white fe production workers in a large rubber manufacturing was examined. The cohort consisted of 1,649 white fe production workers who were 40-84 yr old on Janua 1964, and either active or retired as of the same date; 99 of them had at least 10 yr employment service within plant under study. An analysis of the observed and expe numbers of death from numerous causes revealed a sli elevated overall standardized mortality ratio, with an e of deaths from both lung cancer and myocardial infarc and a deficit of deaths from breast cancer. There wer deaths due to cancer of the buccal cavity and pharynx, ca of the liver and intrahepatic bile ducts, Hodgkin's diseas leukemia. About two-thirds of all the women had wo for the longest period of their employment, in the manu ture of industrial products; the remainder were eng mostly in the manufacture of tires. A more detailed ana investigation is required before nonoccupational risk fac such as smoking, can be ruled out. (20 refs)

78-5955 **Cervical Cancer in Younger Women.** (Eng) drews, F. J. (Dept. Clinical Cytology, Brig

eral Hosp., Brighton, Sussex BN2 3EW, England); Line- J. J.; Melcher, D. H. *Lancet* 2(8093): 776-778; 1978.

incidence of cervical cancer was studied among 21,216 hton, England, women from whom cervical smears were ined between May 1974 and May 1975. Of 134 patients hom cervical cancer was detected and histologically con- ed, 78 were < 35 yr old and 4 were < 20 yr old. Most ') of the tumors were in situ carcinomas. Abnormal ars and histologically malignant cervical cancers peaked ges 26 to 30; however, abnormal smears and cancer were nd in 24 patients aged 16-19 yr. The mean age of Brighton ents with cervical carcinoma was 50 yr in 1967 and 40 n 1974. Until the etiology of this cancer is established, all ng women should be encouraged to have cervical smears. refs)

5956 **Mortality from Carcinoma of Cervix Uteri in Britain.** (Eng) MacGregor, J. E. (Cytology Unit, ot. Pathology, Univ. Aberdeen, Aberdeen, Scotland); Tep- S. *Lancet* 2(8093): 774-776; 1978.

e-related trends in the incidence of mortality from cervical cer in England, Wales, and Scotland were studied. For nen aged 35 yr or more, mortality from this cancer de- ed in Britain and Wales between 1968 and 1976. A similar nd was observed in Scotland, and the death rates were er for two areas with established screening programs rampian and Tayside) than for the rest of the country. wever, the mortality rates among English and Welsh men < 35 yr old increased between 1968 and 1976. A simi- pattern was observed for Scotland when the data for ampian and Tayside were disregarded. Until cervical can- is better understood, broad-based screening, as practiced hese two areas of Scotland, is probably justified. (10 refs)

-5957 **Hysterectomy-Rates and Cervical Cancer (2 Letters to Editor).** (Eng) Rhodes, P. (35 Elm- ld Road, Newcastle upon Tyne NE3 4BA, England); acgregor, J. E. *Lancet* 2(8097): 1000; 1978.

ne fall in cervical cancer mortality might be partly due to increasing hysterectomy rate and an attendant decrease the population at risk. However, in the sample previously ported, there was no change in the number or age-distribu- on of hysterectomies. Most were done on older women of per social class; this group is at relatively low risk for cervi- l cancer. (no refs)

3-5958 **Adenocarcinoma of the Uterine Cervix in Jewish Women. A Distinct Epidemiological Entity.** Eng) Menczer, J. (Dept. Obstetrics-Gynecology, Chaim neba Medical Center, Tel Hashomer, Israel); Modan, B.; Oelsner, G.; Sharon, Z.; Steintiz, R.; Sampson, S. *Cancer* 41(6): 2464-2467; 1978.

To determine whether the etiology of adenocarcinoma of the uterine cervix (AUC) differs from that of squamous cell carcinoma (SUC), the records of 532 Israeli Jewish women with cervical cancer diagnosed between 1961 and 1971 were examined. The mean annual incidence of invasive cervical cancer among Israeli Jews during the 11-yr period was 4.2/100,000. AUC was diagnosed in 52 women, SUC in 441, and cancers of other histological subcategories in the remainder. The relative frequency of AUC increased steadily with age, from 6% among those aged 20-39 yr to 15% in those aged 70 yr or more. The incidence of SUC was significantly higher in women born in North Africa than in those of other ethnic groups. However, there were only minimal ethnic differences in the incidence of AUC. The incidence of AUC decreased by 50% during 1966-1971, compared with the incidence during 1961-1965, and the incidence of SUC decreased by 24%. The findings support the contention that the etiologies of AUC and SUC are different. (19 refs)

78-5959 **Role of Cu-IUD in Cervical Carcinogenesis: A Follow Up of 36 Months.** (Eng) Luthra, U. K. (Cytology Section, Indian Registry Pathology, ICMR, Maulana Azad Medical Coll., New Delhi-110002, India); Mi tra, A. B.; Prabhakar, A. K.; Bhatnagar, P.; Agarwal, S. *Indian J Med Res* 68: 78-83; 1978.

Cytological monitoring of the female genital tract was performed in 2,603 Indian women who were registered as having had copper-containing intrauterine devices (IUD) inserted. Detailed cytologic analyses were made of 2,244 women who had adequate preinsertional exocervical smears. The rate of dysplasia in these women at the onset of use of the IUD was 2.5%; at 12, 24, and 36 mo, the rates were 2.5%, 2.3%, and 6.3%, respectively. No difference in the rate of dysplasia after the use of the IUD was observed in women who had either negative or inflammatory initial smears. Among 59 dysplasia cases followed, 49 regressed to a normal condition and 10 persisted as dysplasia. No dysplastic lesion progressed to higher grades of dysplasia or to carcinoma during the study period. The above data indicate that continued use of copper-containing IUD for up to 36 mo produces no adverse effect on female genital tract epithelium. (13 refs.)

78-5960 **Risk Factors in Scrotal Epithelioma.** (Eng) Fay, H. T. (Works Medical Office, Renold Ltd., Didsbury, Manchester 20, England). *J R Soc Med* 71(10): 741-747; 1978.

The occurrence of 6 cases of squamous cell carcinoma of the scrotum, 5 fatal, plus 10 cases of forearm keratoses in employees of a light engineering factory between 1955 and 1975

prompted an investigation of possible occupational risk factors responsible for this unusual concentration. The length of employment ranged from 17-38 yr. The keratoses, which are considered a premalignant condition, developed due to exposure of the forearms to mineral oil. These men should be regarded as having a higher risk of developing scrotal cancer. The use of neat cutting oils and the use of oil reclamation plants at the factory are implicated in the scrotal cancer cases. These plants cannot be expected to remove any polycyclic aromatic hydrocarbons (PAH) formed during prolonged use of neat oils. Results of analyses of new, used, and reclaimed oils for PAH in three different laboratories are given. They show that the prolonged use of neat cutting oils and of conventional oil reclamation plants leads to a dangerous accumulation of carcinogens such as benzo(a)pyrene. Other possible risk factors considered are genetic factors, personal hygiene, protective clothing, and the high ambient temperatures in the machine shops. (26 refs)

78-5961 **Epidemiologic Characteristics of Urinary System Tumors and Balkan Nephropathy in an Endemic Region of Bulgaria.** (Eng) Nicolov, I. G. (Inst. Oncology, Medical Acad., Sofia 1156, Bulgaria); Chernozemsky, I. N.; Petkova-Bocharova, T.; Stoyanov, I. S.; Stoichev, I. I. *Eur J Cancer* 14(11): 1237-1242; 1978.

The epidemiologic similarity between endemic nephropathy (EN) and urinary tract tumors (UTT) (especially neoplasms of the renal pelvis and ureter) in an endemic region of Bulgaria (Vratza district) was investigated. These two disorders correlated geographically, had high incidence rates, showed a familial aggregation, and predominated in women and middle-aged people. In hyperendemic villages, the annual age-adjusted incidence rates per 100,000 were 43.5 in men and 74.2 in women for tumors of the renal pelvis and ureter and 38.7 and 24.6, respectively, for tumors of the urinary bladder. UTT were often multiple, especially in EN patients, and generally originated in the uroepithelium. Among UTT patients, 27.3% also had EN, and UTT were found in 6.5% of EN patients. Among patients with both EN and UTT, the former occurred first in 51% of the cases vs the latter in 18% of the cases. It is concluded that the epidemiologic similarity between EN and UTT, their location in the urinary system, and the fact that they frequently occur in combination is proof of a close etiological and pathological relationship. (23 refs)

78-5962 **Etiological Factors Involved in Primary Hepatocellular Carcinoma in Abidjan (Ivory Coast).** (Fre) Le Bras, M. (Service de Clinique Medicale, C.H.U. de Treichville, Abidjan, Ivory Coast); Ticolat, R.; Clerc, M.; Loubiere, R.; Beda, B.; Bertrand, E. *Gastroenterol Clin Biol* 2(8/9): 679-688; 1978.

Etiological factors related to the development of hepatocellular carcinoma (HC) were analyzed in 252 Ivory Coast patients diagnosed in the period 1972-1974. HC repres 13.6% of liver diseases observed in patients hospitalized ing this period. There was no significant correlation with etic factors (blood group or Hb type), season when adm alcoholism, or history of hepatitis (only 8%). The rat men to women was 5.4/1, compared with the overall hos admission ratio of 1.5/1. Hepatitis B surface (HBs) an was found in the serum of 42% of the 50 HC patien whom it was measured, a higher percentage than that i tients with cirrhosis without HC or hepatitis. Cirrhosis associated with HC in 77.3% of the patients. Geograph peared to be an etiological factor since two-thirds of th tients lived in the savannah rather than forest areas. Pat who were workers or farmers from lower economic l outnumbered patients from other social and profess categories. It is concluded that environment may play a in development of HC in the Ivory Coast. (41 refs)

78-5963 **Occurence of Cirrhosis and Primary Liver cer in an Eskimo Population Hyperendemi Infected with Hepatitis B Virus (Meeting Abstract).** (Skinhoj, P. (Dept. Infectious Diseases, Rigshospit Copenhagen, Denmark); Hansen, J. P.; Nielsen, N. H.; kelsen, F. *Dan Med Bull* 25(5): 223; 1978. (no refs)

78-5964 **Epidemic of Toxic Hepatitis in India of Pos Mycotoxic Origin.** (Eng) Tandon, H. D. (D Pathology, All India Inst. Medical Sciences, New hi-110016, India); Tandon, B. N.; Ramalingaswami, V. *Pathol Lab Med* 102(7): 372-376; 1978.

An epidemic of liver disease characterized by onset with fever, rapidly progressive jaundice, and ascites occurre a rural area of India. Several hundred people were affe and mortality was high. The epidemic was heralded by appearance of similar features in the village dogs. Liver b sy specimens from eight patients and autopsy material f one patient and two dogs were studied histologically. characteristic features were centrizonal scarring, hepati nous occlusion, ductular proliferation and cholestasis, f syncytial giant cell transformation of hepatocytes, and cellular fibrosis. Toxic quantities of aflatoxin B_1 were fo in corn samples from the local food stores. The etiolog the disease could not be established unequivocally, bu latoxins, perhaps in combination with other factors, have been the cause. (36 refs)

78-5965 **Hepatoma Risk Among HBsAG Carr (Meeting Abstract).** (Eng) Beasley, R. P. (U Washington, St. Louis, MO); Lin, C. C. *Am J Epider* 108(3): 247; 1978. (no refs)

5966 **A Statistical Analysis of Mortality Due to Liver Cancer and Liver Cirrhosis in Yamanashi Pre-ure, Japan, with Special Emphasis on Relationship to the valence of Schistosomiasis.** (Jpn) Inaba, Y. (Dept. Hy-e and Preventive Medicine, Faculty Medicine, Univ. yo, Bunkyo-ku, Tokyo 113, Japan); Takahashi, E. Y.; uchi, N. *Jpn J Public Health* 24(12): 811-815; 1977.

1970-1975 mortality data for liver cancer and liver cirr-s in Yamanashi Prefecture, Japan, were analyzed, and, iew of the fact that this prefecture contains an area en-ic for schistosomiasis (SSM), an attempt was made to rmine if the data were related to the occurrence of SSM. re were 704 deaths due to liver cancer during this period; vever, the rate of primary liver cancer (4.7%) was signifi-tly lower than the national rate (8.2%). There were 990 ths due to cirrhosis, including 17 cases (1.7%) of alcoholic r cirrhosis, a figure significantly lower than that for the on (3.7%). The age-specific mortality rate for both liver cer and liver cirrhosis was relatively high in the elderly, pared with the national figure, but mortality due to liver hosis was relatively low for men in their fifties. During study period, the geographic distribution of age-adjusted tality due to both conditions correlated significantly with prevalence of SSM in 1948-1952. The standardized mor-y ratio (SMR) of liver cirrhosis in the area endemic for M was signficantly high, but the ratio for the nonendemic a was almost the same as the national ratio. However, the R of liver cancer in the endemic area was approx 50% her than that of the national figure. These findings indi-e that the higher mortality due to liver cirrhosis in nanashi Prefecture is caused by SSM but that due to liver cer is caused by SSM and other unknown etiological fac-s. (6 refs)

5967 **Angiosarcoma of the Liver in Vinyl Chloride/-Polyvinyl Chloride Workers: 1977 Update of NIOSH Register.** (Eng) Spirtas, R. (Illness Effects Sec-n, SB/DSHEFS/NIOSH, Robert A. Taft Labs., 4676 Co-mbia Parkway, Cincinnati, OH, 45226); Kaminski, R. *J cup Med* 20(6): 427-429; 1978.

ta on 64 cases of angiosarcoma among vinyl chloride (VC) ymerization workers reported as of October 1977 are sum-rized. The material comprises 23 US and 41 foreign cases m 11 different countries. The age at diagnosis ranged from to 71 yr, with a median of 49 yr. The latency period ranged m 9 to 38 yr (median of 21 yr), duration of exposure from o 31 yr (median of 18 yr). The data suggest that the report-VC-induced angiosarcoma cases gradually increased over e. The 20- to 30-yr lag between the growth of the industry er World War II and the increase in the number of diag-sed angiosarcomas among VC/polyvinyl chloride (PVC) rkers during the 1970's roughly coincides with the median ency period of 21 yr. Recent studies have also found VC be associated with excesses in brain cancer and neoplasms the respiratory and lymphatic systems. (6 refs)

78-5968 **Epidemiologic Investigation of Employees Chronically Exposed to Methylene Chloride. Mortality Analysis.** (Eng) Friedlander, B. R. (Health, Safety and Human Factors Lab., Eastman Kodak Co., Rochester, NY, 14650); Hearne, T.; Hall, S. *J Occup Med* 20(10): 657-666; 1978.

The 1964-1976 mortality experience of a relatively large male employee population that had been working with methylene chloride on a continuous basis for up to 30 yr was studied. The mortality of the study group was consistent with industrial controls and less than that in the New York State general population. The number of deaths due to malignant neoplasms was significantly less (7) than the number expected for industrial controls (12.5) and New York State controls (16.2). (47 refs)

78-5969 **Cohort Study of the Causes of Death in Ethylene Oxide Production Workers (Letter to Editor).** (Swe) Bengtsson, G. (Orebro, Sweden); Hogstedt, C.; Rohlen, O.; Berndtsson, B. S.; Axelson, O.; Ehrenberg, L. *Lakartidningen* 75(38): 3285-3287; 1978.

Causes of death were determined in 66 workers (Group A) with no exposure to ethylene oxide (EO), 86 workers (Group B) with occasional exposure, and 86 workers (Group C + D) who had been exposed to EO for at least 1 yr 10 or more yr earlier. Other substances to which the workers in Groups C + D and B were exposed were ethylenechlorhydrine (5 mg/m^3), ethylene chloride (100 mg/m^3), bis(2-chloroethyl)ether (0.05 mg/m^3), and ethylene (600 mg/m^3). The overall mortality was 23/89 in Group C + D, 14/86 in Group B, and 10/66 in Group A. Tumors were the cause of death in 9/89 in Group C + D subjects; they included gastric cancer (3 cases), cancer of the large intestine (1 case), malignant melanoma (2), kidney cancer (1), chronic lymphocytic leukemia (1) and acute myeloid leukemia (1). The expected tumor mortality was 3.6 for all tumors, 0.4 for gastric cancer, and 0.14 for leukemia. The differences between the expected and the observed incidence of gastric cancer and leukemia were statistically significant ($p < 0.01$). Tumors were the cause of death in 3/86 Group B subjects and 1/66 Group A subjects. The observed cancer mortality in these groups did not differ significantly from the expected mortality. The findings indicate a significant risk of gastric cancer and leukemia in the workers exposed to EO. (21 refs)

78-5970 **Cancer from Burn Scars.** (Por) Sucena, R. C. (Servico de Queimados do Hospital das Clinicas, FMUSP, Sao Paulo, Brazil). *An Paul Med Cir* 104(3): 203-226; 1978.

The malignant transformation of burn scars was studied in the 103 patients (68 men, 35 women) among 20,194 burn victims in whom this process occurred. The period between

the burn and tumor formation ranged from < 1 yr (1 patient) to > 61 yr (3 patients). Epidermoid carcinoma was diagnosed in 94 patients (Stage I in 20, Stage II in 49, Stage III in 11, and Stage IV in 14), epidermoid carcinoma + basal cell carcinoma in 1, epidermoid carcinoma + fibrosarcoma in 1, and fibrosarcoma in 7. The tumor was localized to the head in 6 patients, to the trunk in 25, to the upper limbs in 37, and to the lower limbs in 35. The time required for cicatrization of the burn wound was 1-3 mo in 28 patients, 4-6 mo in 23, 7-12 mo in 24, 13-60 mo in 19, and > 60 mo in 9. The initial thermal shock, slow cicatrization, and secondary trauma are believed to play etiological roles in the malignant transformation of burn scars. (20 refs)

78-5971 **Concurrence of Bronchial Carcinoma and Anthracosilicosis in the Lung. Silicotic Carcinoma in Scar Tissue of the Lung.** (Ger) Bohm, E. (Pathologisches Inst., Hunscheidtstrasse 1, D-4630 Bochum, W. Germany). *Med Klin* 73(18): 659-663; 1978.

The existence of a causal relationship between anthracosilicosis and bronchial carcinoma was explored by evaluating the autopsy records of 3,452 miners with silicosis, 551 miners without silicosis, and 605 nonminers. Of the total of 4,608, there were 501 cases of bronchial carcinoma, 425 of which were associated with silicosis. The incidence of both afflictions was not related to the length of employment, and there was not correlation between the severity of anthracosilicosis and frequency of cancer incidence. Of the concurrent cases, 2.8% were diagnosed as silicotic carcinoma of the scar tissue, with another 6.8% as possible; only in these cases did a causal relationship seem probable. Histologically, 52.9% of the 425 carcinomas were diagnosed as the squamous epithelial type, 28.7% as the small cell type, and 2.1% as polymorphocellular carcinoma; 37.6% of the tumors metastasized to the adrenal gland, 35.3% to the liver, and 24.2% to the spine. (24 refs)

78-5972 **Radiation-related Thyroid Carcinoma.** (Eng) Cerletty, J. M. (Milwaukee County General Hosp., 8700 W. Wisconsin Ave., Milwaukee, WI, 53226); Guansing, A. R.; Engbring, N. H.; Hagen, T. C.; Kim, H. J.; Shetty, K. R.; Rosenfeld, P. S.; Wilson, S. *Arch Surg* 113(9): 1072-1076; 1978.

Evaluatory studies were conducted on 1,825 subjects who had a history of head or neck irradiation. Thyroid abnormalities were found in 358 of these subjects: single or multiple thyroid nodules in 165, diffuse thyromegaly in 153, and previous thyroid surgery in 40. These 40 previous surgery patients were excluded from further study. Surgery was performed on 113 patients with thyroid nodules, and thyroid carcinoma was found in 34 (papillary adenocarcinoma in 17, mixed papillary-follicular type in 10, follicular type in 6, and a mixed papillary-follicular carcinoma in 1). Clinical examination of the neck was the most valuable method of detecting abn malities. Detection of nodules was not enhanced significar by thyroid imaging studies. Thyroid function studies were helpful in determining thyroid abnormalities, and they w discontinued after 500 patients. A defect in the dela hypersensitivity response was not demonstrated. (17 refs

78-5973 **Malignancies in Portuguese Thorotrast tients.** (Eng) Horta, J. (Faculty Medicine, Ur Lisbon, Lisbon, Portugal); Horta, M. E.; Motta, L. Tavares, M. H. *Health Phys* 35(1): 137-151; 1978.

Partial results of a follow-up study of 1,237/2,434 individu who received Thorotrast in Portugal, mostly from 1930 1950, are reported. As of March 1974, 931 of these patie had died: 16 from local Thorotrast granulomas, 25 from li cirrhosis or fibrosis, 121 from malignant solid tumors (cluding 6 on the edge of large Thorotrast deposits, 75 tum of the liver and other reticuloendothelial tissues, 5 bronch carcinomas, and 4 bone tumors), and 23 from fatal blo diseases (including 12 leukemias). Hemangioendothelion were the most frequently diagnosed tumors in the Thorotr patients; cholangiocarcinomas of the liver were also num ous. The Thorotrast patients, compared with a control gro of 829 individuals injected with a nonradioactive contr drug and with the general Portuguese population, had increased incidence of liver, bone, and lung tumors and l kemias. (23 refs)

78-5974 **Melanoma of the Skin in New Jersey.** (E Stein, D. (Dept. Preventive Medicine and Co munity Health, New Jersey Medical Sch., Coll. Medicine a Dentistry New Jersey, Newark, NJ, 07103); Thind, I. Louria, D. B. *J Med Soc NJ* 75(5): 391-393; 1978.

The incidence of malignant melanoma of the skin in reside of Newark and Morris and Hunterdon Counties, New Jers between 1970 and 1974 was determined and compared w the incidence rates from the Connecticut tumor registry a the Third National Cancer Survey. Because only five ca of cutaneous melanoma were noted in New Jersey blac they were excluded from the rest of the survey. Data fr New Jersey, Connecticut, and the National Cancer Surv showed a progressive increase in age-specific incidence w increase in the age of the patients in both sexes. Relativ few cases occurred before the age of 40. For males in Mor County, the age-specific incidence increased from 0 for th aged 0-9 yr to 20.90 for for those > 80 yr of age; simil increases were found for both sexes in the other areas studi The age-adjusted incidence rates for men were 2.78 in Ne ark, 3.59 in Morris County, 4.59 in Hunterdon County, 5. in Connecticut, and 4.6 in the National Cancer Survey. T age-adjusted incidence rates for women were 2.14 in Newa 6.51 in Morris County, 2.35 in Hunterdon County, 4.65 Connecticut, and 4.4 in the National Cancer Survey. (21 re

5975 **Skin Cancer and Ultraviolet Radiation.** (Eng) Rundel, R. D. (Space and Life Sciences Direc-ate, Natl. Aeronautics and Space Admin., Lyndon B. nson Space Center, Houston, TX, 77058); Nachtwey, D. *Photochem Photobiol* 28(3): 345-356; 1978.

model for calculating the increased incidence of non-lanoma skin cancer in Caucasians resulting from ozone luction is presented. Third National Cancer Survey data skin cancer incidence as a function of age were used to ive a dose-response model that was then used to predict effects of increased biologically harmful UV radiation HUV) resulting from ozone reduction. A biological am-fication factor was calculated separately for each geo-aphic region for which skin cancer incidence data were ailable. Use of the latitudinal variation of incidence was us avoided. The model postulates that the probability of st incidence of skin cancer is distributed log-normally as function of total accumulated lifetime dose of BHUV and at for any given location, this dose to an individual is pro-rtional to his age. The effect on skin cancer incidence of increase in BHUV can then be calculated directly from e extent to which each individual's lifetime accumulated se is thereby increased. The av result of such a perturbation ould be to cause skin cancer to appear to an earlier age. nce skin cancer is predominantly a disease of the elderly, is shift to younger ages has the effect, when integrated over e entire population, of increasing the overall total number cases of skin cancer. For the US as a whole, it is estimated at a 1% permanent decrease in the av stratospheric ozone ickness, which produces about a 2% increase in BHUV, ould ultimately lead to an 8% increase in skin cancer inci-nce. (30 refs)

3-5976 **Background Dose Rate and Leukemia Mortality in Japan.** (Jpn) Sakka, M. (Tohoku Univ. ch. Medicine, Sendai, Japan). *Nippon Acta Radiol* 38(3): 72-276; 1978.

The relationship between the natural background radiation dose and leukemia mortality in 27 Japanese prefectures was studied by linear regression analysis. No linear dose-effect relationship could be demonstrated over the range studied. (9 refs)

78-5977 **Characterization of Normal Human Embryo Cells Grown to Over 100 Population Doublings.** (Eng) Poiley, J. A. (Chemical Carcinogenesis Program, NCI, Frederick Cancer Res. Center, Frederick, MD, 21501); Schuman, R. F.; Pienta, R. J. *In Vitro* 14(5): 405-412; 1978.

Normal human embryo fibroblasts were subcultured for > 100 population doublings in unmodified basic medium. Their growth rate, confluent density, chromosome stability, growth in soft agar, ability to hydrolyze casein, and tumorigenicity indicated that they possessed the characteristics of normal cells. The batch of fetal bovine serum used to supplement the medium was of primary importance in the long-term growth of this culture. (32 refs)

See also:
*(Rev.): 78-5401, 78-5402, 78-5403, 78-5404, 78-5406, 78-5411, 78-5414, 78-5423, 78-5425, 78-5426, 78-5429, 78-5431, 78-5432, 78-5435, 78-5447, 78-5459, 78-5460, 78-5461, 78-5462, 78-5463.
*(Chem.): 78-5486, 78-5489, 78-5501, 78-5537, 78-5549, 78-5555, 78-5615, 78-5629.
*(Phys.): 78-5715, 78-5718, 78-5719, 78-5720, 78-5729.
*(Viral): 78-5785, 78-5790, 78-5822, 78-5835, 78-5836, 78-5837.
*(Path.): 78-5875.

78-5978 **Repopulation of Denuded Tracheal Grafts with Normal, Preneoplastic, and Neoplastic Epithelial Cell Populations.** (Eng) Terzaghi, M. (Biology Div., Oak Ridge Natl. Lab., P.O. Box Y, Oak Ridge, TN, 37830); Nettesheim, P.; Williams, M. L. *Cancer Res* 38(12): 4546-4553; 1978.

In vivo growth characteristics of nonmalignant and malignant epithelial (ept) cell cultures maintained in vitro for various lengths of time were studied. Three types of ept cell cultures from Fischer 344 rats were used: primary cell cultures and two established tracheal cell lines, one neoplastic (BP_1) and the other (1000 M) preneoplastic at passage 7 and neoplastic at passage 20. The cultures were inoculated into isolated tracheas that were then grafted to syngeneic recipients. At least 10^4 ept cells were required to reestablish a complete ept lining in denuded tracheal grafts, whether normal or tumorigenic cell cultures were used. Inoculation of denuded tracheas with 1-wk-old primary cultures of normal tracheal epithelium resulted in reestablishment of a nearly normal mucociliary tracheal lining within 1-2 wk. Injection of primary ept cultures older than 1 wk failed to reestablish an ept lining; instead, the tracheal lumen became obliterated with connective tissue. In immunosuppressed recipients, inoculation with the preneoplastic (passage by) cell line resulted in the establishment of a well-organized, keratinizing squamous epithelium that remained stable for at least 6 wk if the recipient was immunosuppressed but was rejected at 4 wk in immunocompetent hosts. Inoculation with line 1000 M at passage 20 resulted in the establishment of a well-organized squamous epithelium for 3-4 wk and the development of disorganization, exophytic growth, and invasion at 4-6 wk. This occurred only in immunosuppressed recipients. In immunocompetent recipients, the ept lining was completely rejected within 2 wk. When cells from the highly malignant squamous cell carcinoma line (BP_1) were inoculated into trachea with an intact ept lining, only a few isolated nests of malignant cells were observed at 6 wk. Repopulation of denuded tracheas with cells from the same tumor line resulted in the establishment of an atypical squamous lining at 1 wk. At 2 wk, invasion was widespread, resulting in destruction of the trachea grafts shortly thereafter. The results show that this new "in vivo culture system" is suited to study of the growth and differentiation of carcinogen-altered or preneoplastic ept cells. It will complement existing in vitro culture systems. (27 refs)

78-5979 **Selection and Biologic Properties of Malignant Variants of a Murine Lymphosarcoma.** (Eng) Brunson, K. W. (Dept. Developmental and Cell Biology, Univ. California, Irvine, CA, 92717); Nicholson, G. L. *J Natl Cancer Inst* 61(6): 1499-1503; 1978.

The murine lymphosarcoma cell line RAW117 was use
a source of parental cells for the in vivo sequential selec
of stable malignant variants in BALB/c mice. Sequentia
vivo selections were performed by iv tumor cell inoculat
removal of resulting solid liver tumor nodules for growt
vitro, and reinjection of the cultured cells iv. After 10 s
sequential selections for implantation, invasion, survival,
growth in liver, a lymphosarcoma cell line was obtai
(RAW117-H10) that formed 200-fold more gross liver tu
nodules than did the parental tumor cell line in compara
biologic assays and displayed enhanced malignant proper
when monitored by time of host death. Very few lung nod
or tumors were present at other sites with either the pare
or any of the selected RAW117 lines. No differences in h
colonization were found between lymphosarcoma-selec
lines cultured for a short term (2 wk) and cell lines cultu
for a long term (3 mo). The enhanced malignancy of
tumor variant probably does not occur by temporal ada
tion of the entire cell population to a different growth e
ronment. Conditions in vivo may have resulted in the en
gence of more aggressive and/or less antigenic vari
sublines from the parental population; this would be cons
ent with a recently proposed model for clonal evolution
neoplasia. (16 refs)

78-5980 ***Hymenolepis nana* in Retroperitoneal Sarco of an Albino Rat.** (Spa) Perez-Arroyo,
(Laboratorio de Investigacion, Hospital Militar Regio
Guadalajara, Jal, Mexico); Lagarriga-Attias, J.; Corrales-S
cedo, A. *Patologia (Mex)* 15(2): 111-117; 1977.

An adult form of *Hymenolepis nana* was found in the c
of an undifferentiated retroperitoneal sarcoma of a laborat
albino rat. The parasitic origin of some tumors is review
The relationship between parasites and the development
neoplasia is not fully understood. (24 refs)

78-5981 **Magnesium in Leukocyte Cells in Relation Leukemogenesis.** (Eng) Hazdra, J. J. (Dept. B
chemistry, Illinois Benedictine Coll., Lisle, IL, 60532); Bu
no, T. J.; Neenan, J. P. *In: Advances in Comparative L
kemia Research 1977. Proceedings of the VIIIth Internatio
Symposium on Comparative Research on Leukemia a
Related Diseases, held in Amsterdam, The Netherlands
22-26 August, 1977.* Bentvelzen, P.; Hilgers, J.; Yohn, D.
eds. (New York: Elsevier/North Holland Biomedical Pres
503 pp.; 320-321; 1978.

Magnesium levels (micromoles/10^9 WBC) were 7.0 in norm
subjects, 5.3 in granulocytic leukemia patients, and 12.37

phocytic leukemia patients. The Mg/ATP ratio was 3.5 ormal WBC, 2.5 in granulocytic WBC, and 10.74 in lym-cytic WBC. There appears to be an inverse correlation veen Mg and ATP in the WBC of the leukemia patients. efs)

5982 **Genetics of Bovine Leukemia. II. Effect of Parents on the Frequency of Leukemia in the geny.** (Rus) Ernst, L. K. (Dept. Genetics and Selection ricultural Animals, Agricultural Inst., Novosibirsk, SR); Petukhov, V. L. *Genetika* 14(7): 1247-1256; 1978.

attempt was made to estimate the heritability of a predisition or resistance to leukemia in cattle. A pedigree anal- of 14,000 animals (progeny of 554 sires), of whom 2,060 leukemia, showed that the contribution of fathers to the kemia morbidity of their daughters ranged from 7% to %. The incidence of leukemia among the offspring of leunic sires was 26.6%, compared with the av leukemia incice of 20.8%. (22 refs)

5983 **Terminal Differentiation of Human Promyelocytic Leukemia Cells Induced by Dimethyl Sulide and Other Polar Compounds.** (Eng) Collins, S. J. (Lab. mor Cell Biology, NCI, NIH, Bethesda, MD, 20014); Russti, F. W.; Gallagher, R. E.; Gallo, R. C. *Proc Natl Acad USA* 75(5): 2458-2462; 1978.

e effect of dimethyl sulfoxide (Me_2SO) on a human leunic cell line (HL-60) established from the peripheral WBC a patient with acute promyelocytic leukemia is reported. is cell line displays a distinct morphological and histoemical commitment toward myeloid differentiation; the ltured cells are predominantly promyelocytes. The addin of Me_2SO (1.25%) to the culture induced these cells to ferentiate into myelocytes, metamyelocytes, and banded d segmented neutrophils. All 150 clones developed from HL-60 culture showed similar morphological differentian in the presence of Me_2SO. Unlike the morphologically mature promyelocytes, the Me_2SO-induced mature cells hibited functional maturity, as exemplified by their phagotic activity. A number of other compounds previously own to induce erythroid differentiation of mouse eryroleukemia (Friend) cells (acetamide, N-methylacetamide, N-dimethylacetamide, N-methylformamide, N,N-dimeylformamide, piperidone, 1-methyl-2-piperidone, and ethylene glycol) induced analogous maturation of the L-60 cells. The marked similarity in behavior of HL-60 cells d Friend cells in the presence of these inducing agents sugsts that similar molecular mechanisms are involved in the duction of differentiation of these human myeloid and mue erythroid leukemic cells. (28 refs)

78-5984 **Clonal Analysis of Chronic Myeloid Leukemic Cells Using Agar Cultures.** (Eng) Metcalf, D. (Cancer Res. Unit, Walter and Eliza Hall Inst., Royal Melbourne Hosp., P. O. 3050, Victoria, Australia); Johnson, G. R.; Kolber, S.; Dresch, C. *In: Advances in Comparative Leukemia Research 1977. Proceedings of the VIIIth International Symposium on Comparative Research on Leukemia and Related Diseases, held in Amsterdam, The Netherlands on 22-26 August, 1977.* Bentvelzen, P.; Hilgers, J.; Yohn, D. S., eds. (New York: Elsevier/North Holland Biomedical Press): 503 pp.; 307-310; 1978.

Myeloblasts in the peripheral blood of chronic myeloid leukemia (CML) patients were capable of forming neutrophilic and eosinophilic colonies. Analysis of feeder layer activity showed that unfractionated CML cells have relatively low feeder layer activity and that both CML and acute ML (AML) cells depend on stimulation for proliferation. AML and CML cells exhibited lower autologous stimulating activity than nonleukemic populations. The results support the concept that in CML, there is extreme hyperplasia of the granulocytic progenitor cells that remain responsive to regulator control. (6 refs)

78-5985 **Growth and Differentiation of Human Myelogenous Leukemia Cells in Conditioned Medium from Human Embryo Cultured Cells.** (Eng) Gallagher, R. (NCI, Bethesda, MD, 20014); Ruscetti, F.; Collins, S.; Gallo, R. *In: Advances in Comparative Leukemia Research 1977. Proceedings of the VIIIth International Symposium on Comparative Research on Leukemia and Related Diseases, held in Amsterdam, The Netherlands on 22-26 August, 1977.* Bentvelzen, P.; Hilgers, J.; Yohn, D. S., eds. (New York: Elsevier/-North Holland Biomedical Press): 503 pp.; 303-306; 1978.

Conditioned medium (CM) from early passage fibroblast cultures of human embryonic origin stimulated extended growth and differentiation in suspension cultures of myeloid cells from patients with myelogenous leukemia. The stimulatory activity probably derives from a subpopulation of embryonic cells since (1) it was not recovered from adult cell cultures, (2) it was infrequent even in embryonic cultures; and (3) it was labile with respect to culture passaging and freezing. The possibility that the active factor(s) interacted with specific leukemic cell receptors (eg, fetal receptors) was suggested by its selective stimulation of myelogenous leukemia WBC and, in some cases, by cytogenetic identification of cultured leukemia cells. The ability of embryonic CM to provide replicating WBC suspension cultures should be of value in studies of myeloid cell differentiation. (7 refs)

78-5986 **Heterotransplantation of the K562 Cell Line Derived from a Patient with Chronic Myeloid Leukemia.** (Eng) Machado, E. A. (Center Health Sciences, Univ. Tennessee Memorial Res. Center, 1924 Alcoa High-

way, Knoxville, TN, 37920); Lozzio, B. B.; Lozzio, C. B.; Aggio, M. *In: Advances in Comparative Leukemia Research 1977. Proceedings of the VIIIth International Symposium on Comparative Research on Leukemia and Related Diseases, held in Amsterdam, The Netherlands on 22-26 August, 1977.* Bentvelzen, P.; Hilgers, J.; Yohn, D. S., eds. (New York: Elsevier/North Holland Biomedical Press): 503 pp.; 418-421; 1977.

Chronic myelogenous leukemia (CML) cells from the K562 cell line, which is positive for the Philadelphia chromosome, were transplanted sc in nude mice. The recipient mice developed solid vascularized tumors termed myelosarcomas. The myelosarcoma cells retained the original chromosome and antigen markers, and they actively incorporated ^{3}H-thymidine. The growth of the myelosarcomas was inhibited by reconstituting the nude mice with isogeneic thymuses. The tumor, which can be maintained by serial passage, provides a useful bioassay system for therapeutic trials and studies of cell kinetics. (7 refs)

78-5987 **Expression of Cholera Toxin Binding Sites on Normal and Malignant Haemopoietic Cells.** (Eng) De Cicco, D. (Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England); Greaves, M. F.; Van Den Engh, G.; Warner, N. L. *In: Advances in Comparative Leukemia Research 1977. Proceedings of the VIIIth International Symposium on Comparative Research on Leukemia and Related Diseases, held in Amsterdam, The Netherlands on 22-26 August, 1977.* Bentvelzen, P.; Hilgers, J.; Yohn, D. S., eds. (New York: Elsevier/North Holland Biomedical Press): 503 pp.; 357-362; 1977.

The expression of G-M1 gangliosides on the surface of normal and malignant hemopoietic stem cells was studied by determining the number of ^{125}I-cholera toxin binding sites per cell. There were no alterations in G-M1 expression that could be correlated with hemopoietic malignancy per se. Preliminary experiments with the Fluorescence Activated Cell Sorter (FACS) indicated that normal immature myeloid cells had a lower density of toxin binding sites than granulocytes. The correlation of G-M1 expression with maturation was also apparent within a single clone of Philadelphia chromosome-positive chronic myeloid leukemia cells entering acute blast crisis. Separation of the cells by FACS according to fluorescence intensity revealed a clear distinction between the relatively mature myeloid elements and the blast cells. Mouse cells had a receptor density two orders of magnitude higher than human lymphoid cells. This difference may explain the previously reported differential effects of cholera toxin on lymphocyte proliferation. (16 refs)

78-5988 **Effect on Androgen Depletion on Growth and Androgen Dependency of Shionogi Carcinoma 115.** (Eng) Kitamura, Y. (Inst. Cancer Res., Osaka U Medical Sch., Kita-ku, Osaka, 530, Japan); Okamoto, Uchida, N.; Yamaguchi, K.; Matsumoto, K. *Cancer* 38(12): 4711-4716; 1978.

To determine whether the androgen (ADG) dependenc the Shionogi carcinoma 115 (SC115) varies in diffe phases of growth, the fate of SC115 tumors in an ADG-c leted state was studied in DS mice. The SC115 tumors w implanted in castrated male mice, and testosterone propi ate (100 μg, sc) was injected daily for 60 days startin various times after grafting. Inoculated SC115 cells sho evidence of necrosis within 5 days after implantation in absence of ADG. After initiation of growth by ADG, subsequent fate of the tumors following ADG removal pended on the size of the tumor: small, medium, and la tumors showed complete, temporary, and no regression, spectively. In contrast to the partial and complete lack ADG dependence of medium and large tumors in situ, tu seeds taken from the medium and large tumors before AD removal grew only in males when transplanted into male female mice. On the other hand, tumor seeds taken fr about one-half of the regrown tumors after ADG remo grew in both male and female hosts. One type of th ADG-independent tumors contained cytosol ADG recep (AR) and consisted of the original SC115 cells (medull cancer) and spindle-shaped cells. Another type of indepe ent tumor contained no cytosol AR and consisted only spindle-shaped cells. These findings suggest that the effec ADG depletion on growth of the tumor, which consists AR-positive and ADG-dependent cells, varies in differ growth phases and that the ADG dependence of tumor c can be changed after ADG removal. The SC115 tumor see to be a good model for elucidating hormone-dependent c cer growth and for establishing endocrine treatment in h mone-dependent cancers. (26 refs)

78-5989 **Thyroid Disease and Function in Breast Can Patients and Non-hospitalized Controls E luated by Determination of TSH, T3, rT3, and T4 Levels Serum.** (Eng) Adami, H. O. (Dept. Surgery, Uppsala Un Uppsala, Sweden); Rimsten, A.; Thoren, L.; Vegelius, Wide, L. *Acta Chir Scand* 144(2): 89-97; 1978.

Earlier thyroid disease and thyroid function were compar in 179 consecutively diagnosed breast cancer patients and l age-matched controls. Thyroid function was assessed by m suring the serum levels of thyrotropin (TSH), triiodothy nine (T3), reverse triiodothyronine (rT3), and thyroxine (T The overall occurrence of thyroid disease, 15/179 in the p tient group and 17/179 in the control group, was similar, a two women from each group had a history of T4 treatme Slight but significant differences were found in the patie group for three serum hormone levels, with a higher me value for TSH (2.5 milliunits/liter in the patient group vs l.

e controls) and rT3 [0.38 vs 0.33 nanomole(nmol)/liter] a lower mean value for T3 (2.16 vs 2.25 nmol/liter). T4 entration in the serum did not differ significantly. In a lom sample of 50 patients and controls, T3-resin uptake significantly higher in the patient group than in the con- group. The changes in thyroid hormone levels in the st cancer patients were similar to those noted in a number ther nonthyroidal diseases; eg, hepatic cirrhosis, myocar- infarction, acute febrile illness, and starvation. The pat- of changes in the patient group may represent secondary probably extrathyroidal changes in thyroid hormone me- olism. There is no indication that thyroid disease is an logic factor in breast cancer. (53 refs)

5990 **Thyroid-stimulating Hormone and Prolactin Levels in Breast Cancer.** (Eng) Aldinger, K. A. ction Endocrinology and Medical Breast Service, Dept. dicine, Univ. Texas System Cancer Center, M.D. Ander- Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 30); Schultz, P. N.; Blumenschein, G. R.; Samaan, N. A. *h Intern Med* 138(11): 1638-1641; 1978.

um thyroid-stimulating hormone (TSH) and prolactin RL) levels in 148 breast carcinoma (BC) patients were mea- ed by radioimmunoassay before and after iv administra- n of protirelin (PTR: 500 μg). The patients, of whom 42 re premenopausal and 106 postmenopausal, were divided o metastatic or primary cancer groups and matched with normal controls. Basal TSH levels were elevated in 36% the BC patients and basal PRL levels in 22%. Although ferences in mean TSH and PRL levels between the patients d controls were significant, there was no correlation be- een serum levels of the two hormones. Of 53 patients with vated basal TSH, 30 did not demonstrate an elevated peak er PTR stimulation. In the metastatic BC group, 13% of e patients with normal basal PRL responded to PTR stimu- ion. All but two of the patients with elevated basal TSH els had normal serum thyroxine levels and normal T_3 resin take. Previous irradiation to the upper chest area did not fect TSH levels; and although the mean survival and dis- se-free interval were shorter for patients with elevated TSH d PRL, the results were not significant. (39 refs)

3-5991 **Relationship Between Urine and Plasma Estrogen Ratios.** (Eng) Longcope, C. (Worcester oundation Experimental Biology, Shrewsbury, MA, 01545); ratt, J. H. *Cancer Res* 38(11, part 2): 4025-4028; 1978.

n attempt was made to determine whether women with ffering urinary estrogen ratios had different blood produc- on rates (BPR) of the estrogens. Normal young women collected 24-hr urine specimens during the follicular and luteal phases of their cycle, and urinary estrone, estradiol, and estriol levels were measured. The women were placed into two groups according to whether their urinary estrogen ratios were >1.3 or <0.7. Normal postmenopausal women collected 24-hr specimens and were grouped according to whether their ratios were >3.2 or <2.1. An additional group studied without regard to urinary ratios consisted of women who had had breast cancer but had no clinical evidence of the disease. Between the respective high- and low-ratio groups, there were no significant differences in circulating levels of estriol, metabolic clearance rates of estriol, or BPR of estriol, estrone, or estradiol. The breast cancer women and normal controls also had similar BPR of the three estrogens. Ratios of the BPR of estriol to estrone and estradiol were similar in the high- and low-ratio groups and also in the breast cancer and control groups. Therefore, the differences in urinary ratios reflect differences in the pathways of metabolism of the free circulating estrogens and not variations in BPR. Estriol was produced at only 10% the rate of estrone and estradiol and thus would probably play only a minor role in the overall biological activity of the estrogens at the level of the target tissues. (24 refs)

78-5992 **Prolactin and the Development and Progression of Early Neoplastic Mammary Gland Lesions.** (Eng) Welsch, C. W. (Dept. Anatomy, Michigan State Univ., E. Lansing, MI, 48824). *Cancer Res* 38(11, part 2): 4054-4058; 1978.

The effect of chronic suppression of prolactin (PL) on the initiation and progression of hyperplastic alveolar nodules (HAN) was determined in nulliparous 2-mo-old and multiparous 8-mo-old C3H/HeJ mice. Also determined was the growth stimulatory effect of human placental lactogen (HPL), a peptide chemically and physiologically similar to PL, on hyperplastic (benign) human breast tissues. Chronic suppression of PL by 2-bromo-α-ergocryptine (CB-154: 0.1 mg/day for up to 1 yr, sc) sharply suppressed or totally prevented the formation of HAN and neoplastic mammary gland lesions in young mice and markedly suppressed the progression of HAN to carcinomas in mature mice. Most of these mice lived an entire life-span free of mammary tumors, during which they had normal ovarian activity, normal body wt gains, and no signs of morbidity. Treatment of mice with 17β-estradiol or the oral contraceptive Enovid also suppressed HAN development and subsequent mammary tumorigenesis. CB-154-induced PL suppression was more effective than ovariectomy in suppressing HAN development and comparable to this procedure in suppressing mammary carcinoma development. HPL promoted growth both in vitro (organ culture) and in vivo (athymic nude mouse) of the epithelium in benign human breast tumors. Whether or not human pituitary PL is capable of mimicking the mammotrophic action of HPL and whether a dysplastic, PL-sensitive lesion

comparable to HAN exists in the human breast remain to be determined. (16 refs)

78-5993 **A Specific Progesterone-binding Component of Human Breast Cyst Fluid: Its Isolation and Characterization (Meeting Abstract).** (Eng) Pearlman, W. H. (Dept Pharamacology, Univ. North Carolina Sch. Medicine, Chapel Hill, NC, 27514); Peng, L. H.; Mazoujian, G.; Haagensen, D. E.; Wells, S. A.; Kister, S. J. *J Endocrinol* 75(3): 19-20; 1977. (3 refs)

78-5994 **Effect of Serum on Cells Cultured from Human Mammary Tumors.** (Eng) Gaffney, E. V. (Pennsylvania State Univ., 5101 Freer Building, University Park, PA, 16802); Pigott, D. *In Vitro* 14(5): 451-457; 1978.

Cultures established from human mammary ductal carcinomas were studied to determine cell yield from tumors, survival time in primary culture, and the response of the cells to different sera. Clusters of the cells formed two morphologically distinct epithelial colonies in culture, E and E′. From 0.3% to 13.0% of E′ cell clusters attached and formed colonies. Attachment was independent of tumor grade. The survival of E′ cell colonies was limited to 10 days with rapid cell degeneration commencing at 7 days. A comparison of sera (fetal bovine, agamma bovine, whole bovine, human, swine, horse, and chicken) showed that colony formation by the cells during the first week of culture was max in the presence of fetal bovine serum (FBS). Human serum alone was 70%-100% less effective in promoting E′ colonies. In the presence of FBS, human serum from normal donors inhibited colony development with E′ but not with E cells. This inhibitory activity could not be attributed to either antagonistic hormones or the source of human serum. The results indicate that normal human serum contains a factor that exhibits an inhibitory activity specific for E′ human epithelial cells derived from malignant tumors. (16 refs)

78-5995 **Inhibition of Pregnancy-dependent Mammary Tumorigenesis by a Single Treatment of Neonatal GR/A Mice with Monosodium Glutamate.** (Eng) Nagasawa, H. (Pharmacology Div., Natl. Cancer Center Res. Inst., Tsukiji 5-1-1, Chuo-ku, Tokyo, 104, Japan); Yanai, R. *Proc Soc Exp Biol Med* 158(1): 128-129; 1978.

The effects of neonatal administration of monosodium gl mate (MSG) on the development of pregnancy-depend mammary tumors and on reproduction were examine GR/A mice. A single sc injection of 4 mg MSG was gi on the day of birth. Mice were mated on day 60, and li size and number of palpable mammary tumors were cou at parturition. MSG treatment markedly inhibited the pearance of pregnancy-dependent mammary tumors and creased the number of tumors per mouse. Reproduction not affected. These results suggest that the developmen pregnancy-dependent mammary tumors is affected to a gr er extent by subtle changes in the hormonal milieu, especi in progesterone level, than is the maintenance of pregna (13 refs)

78-5996 **Multicellular Tumor Spheroid Formation Breast Cancer Cells Isolated from Diffe Sites.** (Eng) Yuhas, J. M. (Cancer Res. and Treatment ter, Univ. Mexico, 900 Camino de Salud N.E., Albuquer NM, 87131); Tarleton, A. E.; Molzen, K. B. *Cancer* 38(8): 2486-2491; 1978.

The possibility that strong natural or artificial selectio growth in suspension might produce lines that are unabl form multicellular tumor spheroids (MTS) was investig using breast cancer lines derived from malignant pleural sions or from solid growths. Cells from 14 breast cancer l (8 human, 5 rat, and 1 mouse) were plated in liquid med over an agar medium base. Within 1-3 wk, 8/14 lines for MTS, and all of these had been isolated from solid tu or metastases. The remaining six lines, which were isol from malignant pleural effusions, failed to form MTS with one exception, failed to form aggregates > 10-50 The exception formed aggregates of up to 100 μm, but failed to grow and rapidly degenerated. Similarly artif selection for an ascites variant of the MTS-forming rat 1 adenocarcinoma line produced the 13762-A line, which no longer form MTS. These results suggest that breast ca cells from pleural effusions are genetically different most tumor cells in solid breast cancer specimens, that are unable to grow in true solid form, and that these di ences persist in spite of prolonged propagation in tissue ture. (19 refs)

78-5997 **Population Density as a Factor in the Evolu of Neoplastic Cell Lines.** (Eng) Taylor, W (Lab. Cellular and Molecular Biology, NCI, Building Room 4D-18, Bethesda, MD, 20014); Camalier, R. F.; T

R. W.; Sanford, K. K. *Cancer Res* 38(11, part 1): 0-3846; 1978.

role of population density in the progression from the neoplastic to the neoplastic state was studied in two ed nonneoplastic mouse cell lines, NCTC 7914 and 7915. o sublines from each clone were transferred every 3-4 days noculum sizes selected to minimize or maximize cell-cell tact, 1 x 10^5 or 4 x 10^5 cells/flask. In vivo assays of norigenicity were made at 3-mo intervals. Tumor produc- was observed in all lines, regardless of inoculum size. wever, sublines carried at the high inoculum size produced nors with significantly shorter latent periods than those ried at the low size. By passage 55, 85%-100% of the onies were diagnosed morphologically as neoplastic. By days in vitro, all sublines grew in agarose as colonies ≥ mm in diameter, but the number of colonies was greater sublines grown at the higher inoculum size than those wn at the lower size. Cells derived from the neoplastic lines were susceptible to BCG-activated macrophages; the gree of susceptibility increased as the tumor latent period reased. The parent clones did not form colonies in aga- e, nor were they killed by activated macrophages. Satura- n density increased and population doubling time de- ased with period in culture. There was no increase in obic glycolysis with time in culture or neoplastic transfor- tion. The results indicate that carrying mouse cells at low nsity does not prevent neoplastic transformation and that tain morphological changes, growth in agarose, and sus- ptibility to activated macrophages are associated with neo- astic transformation. (14 refs)

3-5998 **An Electronic Theory of Cancer.** (Eng) Szent-Gyorgyi, A. (Workshop Natl. Foundation r Cancer Res., Marine Biological Lab., Woods Hole, MA). nt *J Quantum Chem* 12(Suppl 1): 407-414; 1978.

he history of life is divided into two parts by the appearance f light: an anaerobic, dark proliferative period (α) and an erobic period of light-regulated growth (β). The transition etween the two ($\alpha <--> \beta$) is still an everyday occurrence. lowever, a cell may lose its ability to build up and stabilize s β state and may thus return permanently to the prolifera- ve α state; this state is cancer, characterized by a low cohe- on and proliferation. Thus, the cancer problem may be oiled down to the chemical mechanism of the $\alpha <--> \beta$ ansformation. The central event of this transformation is ne electronic desaturation of protein, the first step of which s production of an electron acceptor that can take over the lectrons from the protein. The proposed acceptor is methyl- lyoxal. The formation of a charged radical in the processes onnected with the electronic desaturation of proteins is voided by incorporating the methylglyoxal into the donor rotein molecule before transferring charges. The incorpora- tion of methylglyoxal is essentially a *p*-type doping. This view suggests that the cancer problem is indeed finite. (15 refs)

78-5999 **Thermographic Tumor Detection Enhancement Using Microwave Heating.** (Eng) Thompson, J. E. (Coll. Engineering, Univ. South Carolina, Columbia, SC, 29208); Simpson, T. L.; Caulfield, J. B. *Trans Microwave Theory Tech* 26(8): 573-580; 1978.

The sensitivity of thermography for tumor detection was shown to be improved by concurrent irradiation of the examined area with 2,450-gigahertz microwaves. The microwave radiation increases the temperature differential between healthy and tumor tissue substantially. Strain-2 guinea pigs bearing an sc line-10 hepatoma in the left shoulder were irradiated for 75 sec, and thermographic measurements were made every 15 sec during both irradiation and cooling. Contour maps depicting areas that experienced the same change in temperature were constructed. These maps clearly indicated the tumor location, particularly as the duration of irradiation increased. The max temperature increase in the tumor tissue was 5.5 C, that in healthy tissue was 2.5 C. Although microwave irradiation increased the spatial temperature nonuniformity of all tissue, the max change in the healthy shoulder was 1.5 C, compared with 3.5 C in the tumor. Therefore, increased nonuniformity of the spatial temperature distribution is indicative of an existing tumor. The rates of heating and cooling of the tumor tissue were also greater than those of healthy tissue. The thermal response of breast tumors, which are likely to be less cellular and vascular than hepatomas, is presently unknown. (24 refs)

78-6000 **Use of Computerized Methods to Predict Metabolic Pathways and Metabolites.** (Eng) Spann, M. L. (Natl. Library Medicine, Bethesda, MD, 20014); Chu, K. C.; Wipke, W. T.; Ouchi, G. *J Environ Pathol Toxicol* 2(1): 123-131; 1978.

Computer programs that can predict biologic activities from metabolism of a compound are being developed. The project has two stages: (1) to incorporate metabolic reactions into a computer program to predict probable metabolites and (2) to recognize structural units that may be related to specific biologic activities. Computer analysis may aid in (1) screening compounds to determine if their metabolites are probable carcinogens; (2) identifying unknowns isolated in metabolic studies, and (3) designing appropriate radioactive tracer experiments for elucidating a specific metabolic pathway. (7 refs)

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ABBREVIATIONS

URNAL names are abbreviated according to the *List of Journals Indexed in Index Medicus, Abbreviation ting*. If the journal is not listed in this, abbreviations are derived from the *International List of Periodical Title rd Abbreviations*.

NGUAGE of the article is indicated in parentheses after the title and is represented by a three-letter code. e source for these codes is *MARC Manuals Used by the Library of Congress*, pages 183-187.

BREVIATIONS used in abstracts:

	angstrom(s)
TH	adrenocorticotropic hormone
P	adenosine diphosphate
MP	adenosine monophosphate
P	adenosine triphosphate
prox	approximately
	average
G	bacillus Calmette-Guerin
l	twice daily
	degree(s) centigrade
	calorie(s)
cal	kilocalorie(s)
	cubic centimeter(s)
	curie(s)
nCi	millicurie(s)
Ci	microcurie(s)
n	centimeter(s)
NS	central nervous system
m	counts per minute
NA	deoxyribonucleic acid
D_{50}	median effective dose
DTA	ethylenediamine tetraacetic acid
	gram(s)
g	kilogram(s)
ng	milligram(s)
g	microgram(s)
b	hemoglobin
	hour(s)
	intra-arterial
	intradermal
A	Immunoglobulin A
B	Immunoglobulin B
G	Immunoglobulin G
M	Immunoglobulin M
LS	increased life span
n	intramuscular
	intraperitoneal
U	International Unit(s)
	intravenous
m	Michaelis constant
D	lethal dose
D_{50}	median lethal dose
l	molar
µM	micromolar
mOsm	milliosmolar
max	maximum
mEq	milliequivalent(s)
min	minute(s)
ml	milliliter(s)
µl	microliter(s)
mm	millimeter(s)
mo	month(s)
mol wt	molecular weight
N	normal concentration
NAD	nicotinamide adenine dinucleotide
NADH	reduced nicotinamide adenine dinucleotide
NADP	nicotinamide adenine dinucleotidephosphate
NADPH	reduced nicotinamide adenine dinucleotidephosphate
NCI	National Cancer Institute
NIH	National Institutes of Health
PAS	periodic acid-Schiff
po	orally
ppb	parts per billion
ppm	parts per million
qid	four times daily
qod	every other day
QO_2	oxygen quotient
R	roentgen
RBC	red blood cells (erythrocytes)
RNA	ribonucleic acid
rpm	revolutions per minute
sc	subcutaneous
sec	second(s)
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
soln	solution
TCD	tissue culture dose
TCD_{50}	median tissue culture dose
tid	three times daily
UV	ultraviolet
WBC	white blood cells (leukocytes)
wk	week(s)
wt	weight
X	times
yr	year(s)

6001 **Report of the Conference on Modification of Mutagenic and Carcinogenic Activity, Wilsburg, Virginia, October 24-26, 1977.** (Eng) De Serres, . (Natl. Inst. Environmental Health Sciences, Research ngle Park, NC). *Mutat Res* 54(2): 197-202; 1978.

luation of the results of a joint US/Japanese conference iscuss factors that can modify the mutagenic and/or carogenic activity of environmental chemicals indicated that se factors are wide-ranging and that they include genes, ymes, disease, several compounds, metal ions, sex hornes, and vegetable extracts. (no refs.)

6002 **Occupational Carcinogens and Their Interaction with Other Aetiological Factors.** (Eng) Wahouse, J. A. (Regional Cancer Registry, Queen Elizabeth dical Centre, Birmingham, England). *In: Prevention and ection of Cancer. Proceedings of the Third International mposium on Detection and Prevention of Cancer Held by International Study Group for the Detection and Prevenn of Cancer in New York, April 26 - May 1, 1976.* Internaal Study Group for the Detection and Prevention of Can (New York, NY): Vol. 2(Part 1), 2404 pp.; 1601-1608; 8.

dies of occupational carcinogenesis must consider, in adon to duration of exposure to the carcinogen, individual tors (age, sex, ethnic origin, personal hygiene, smoking, oholic intake, and dietary habits), and environmental facs (pollutants in the atmosphere, water or food), climatic l geographic factors, and the urban/rural subdivision. se studies are reviewed that correlate malignancies with ious working situations. A study of bladder cancer incince in the dyestuffs industry showed that the age at onset s related to the age of first exposure. A study of lung cancer asbestos workers indicates a synergistic effect between astos and cigarette smoking. It is also possible for a single stance to act as a multiple carcinogen, as evidenced by a dy relating scrotal epithelioma to industrial mineral oil posure, which also induced primary carcinomas of the nchi, skin and stomach. (8 refs.)

-6003 **Current Views on the Mechanisms of Chemical Carcinogenesis.** (Rus) Pliss, G. B. (N. N. Petrov cological Res. Inst., USSR Ministry Health, Leningrad, SR). *Vopr Onkol* 24(9): 95-107; 1978.

Current concepts on the mechanism of chemical carcinogenesis are reviewed. In the first step of chemical carcinogenesis, the carcinogen is circulated in the body and metabolized. Metabolic activation to an ultimate carcinogen is a characteristic of practically all chemical carcinogens. Enzymes are involved in the metabolism of most carcinogens. In the second step of carcinogenesis, the ultimate carcinogen is bound to the biological substrate (nucleic acids, especially DNA) of the target cells, thereby causing cell damage. Under the effect of carcinogens, the enzyme spectrum often becomes similar to the embryonal enzyme spectrum. The contact of a cell with a carcinogen usually does not lead to immediate formation of a cancer cell, but rather to the appearance of a population of precancer cells whose malignant transformation requires further exposure to carcinogenic or cocarcinogenic factors. (92 refs.)

78-6004 **Chemical Carcinogens: How Dangerous Are Low Doses?** (Eng) Maugh, T. H. (No affiliation given). *Science* 202(4363): 37-41; 1978.

The controversy over the effects of low carcinogen doses on subsequent tumor initiation is reviewed. One view is that the dose-response curve is a straight line; that is, that a tumor can be induced at any dosage. Restated, this is the "one-hit" hypothesis: cancer is a replicable change in cellular genetics resulting from the interaction of one carcinogen molecule with a critical receptor in one cell. The opposing view is that there is a threshold, or no-effect, dose of carcinogen below which tumor initiation occurs only at a chance rate. This view is the one presently held legislatively. The "one-hit" hypothesis is supported by data on radiation-induced cancer, which follows a linear dose-response to an incidence of 0.1%. A review of 151 chemicals studied at several doses in animals showed that none were consistent with a threshold model. Proponents of the threshold hypothesis state that humans are surrounded by carcinogens, and the fact that everyone does not develop cancer indicates there must be protective mechanisms. In fact, compounds such as glutathione and vitamins A and E are able to detoxify small amounts of carcinogens in the body, as long as these systems are not overwhelmed. The body itself needs small amounts of carcinogens, such as heavy metal ions or estrogens, for proper functioning. It is generally accepted that the latent period increases as the dose is reduced. Threshold hypothesis supporters claim that at small doses, the latent period may be longer than the life of the organism. Preliminary results of a large study (the megamouse study) on the effects of low doses of carcinogen indicate that more than one mechanism of carcinogenesis may be operating. (no refs.)

78-6005 The *Salmonella*/Microsome Test for Detection of Carcinogens as Mutagens. (Eng) Ames, B. N. (Dept. Biochemistry, Univ. California at Berkeley, Berkeley, CA, 94720); McCann, J. *In: Prevention and Detection of Cancer. Proceedings of the Third International Symposium on Detection and Prevention of Cancer Held by the International Study Group for the Detection and Prevention of Cancer in New York, April 26 - May 1, 1976.* International Study Group for the Detection and Prevention of Cancer. (New York, NY): Vol. 2(Part 1), 2404 pp.; 2013-2017; 1978.

Advantages of the *Salmonella typhimurium*/microsome test for detecting chemical carcinogens as mutagens are reviewed. Several improvements have made the bacteria orders of magnitude more sensitive than a simple system that just detects reversion of any mutation back to wild-type or a simple forward-mutation system. It is highly probable that chemicals found to be mutagenic in this test will turn out to be carcinogens. (19 refs.)

78-6006 Philadelphia Scientist Suggests an Alternate Way to Detect Nitrosamines. (Eng) Carson, H. C. (No affiliation given). *Household & Personal Products Industry* 15(10): 59-61; 1978.

Differential pulse polarography is proposed as a suitable additional means of detecting nitrosamines and nitrite ion. (3 refs.)

78-6007 Practical and Administrative Aspects of the Use of Carcinogenicity Screening Tests (Letter to Editor). (Dan) Knudsen, I. (Inst. Toxicology, State Food Res. Inst., Denmark). *Ugeskr Laeger* 140(41): 2515-2517; 1978.

The reliability of short-term in vitro carcinogenicity screening tests of chemical substances is reduced by false-positive and false-negative findings. Substances suspect in the in vitro tests cannot be justifiably banned. (15 refs.)

78-6008 Relationship Between Mutagenesis and Carcinogenesis. (Eng) Trosko, J. E. (Dept. Human Development, Coll. Human Medicine, Michigan State Univ., East Lansing, MI); Chang, C. C. *Photochem Photobiol* 28(2): 157-168; 1978.

Genetic influences on the regulation of cell proliferation are discussed, and an integrative theory of carcinogenesis is offered to reconcile the mutation vs epigenetic theories of carcinogenesis, the two-stage theory of carcinogenesis, and Comings' general theory of carcinogenesis. Carcinogenic initiation seems to be the result of the induction of DNA damage, its subsequent error-prone repair and/or replication, and mutation fixation. Carcinogenic promotion appears to involve depression of previously mutated but repressed genes. Th fore, a few neoplasms could arise from a mutagenic ev alone if the mutated gene is in the derepressed state at time of mutation fixation. Many tumors would arise o after there had been a mutagenic event that is followed an epigenetic alteration of these mutated genes (2-stage th ry). Some tumors can arise simply by the abnormal derep sion of genes in tissues at a particular developmental st that prevents the normal regulation of genes that influe cell division. (102 refs.)

78-6009 Volatile Carcinogens: Occurrence, Format and Analysis. (Eng) Hoffmann, D. (Nay Dana Inst. Disease Prevention, American Health Foun tion, Valhalla, NY, 10595); Schmeltz, I.; Hecht, S. S.; Br nemann, K. D.; Wynder, E. L. *In: Prevention and Detect of Cancer. Proceedings of the Third International Symposi on Detection and Prevention of Cancer Held by the Inter tional Study Group for the Detection and Prevention of Can in New York, April 26 - May 1, 1976.* International Stu Group for the Detection and Prevention of Cancer. (N York, NY): Vol. 2(Part 1), 2404 pp.; 1943-1949; 1978.

Carcinogenicity data (humans and animals); levels in occu tional environments, polluted air, and cigarette smoke; a analytical methods for several volatile chemical carcinoge including vinyl chloride, chlorinated hydrocarbons, bis(ch romethyl)ether, N-nitrosamines, and hydrazines, are viewed. (33 refs.)

78-6010 Analytical Methods for Polynuclear Aroma Hydrocarbons. (Eng) Schmeltz, I. (Nayl Dana Inst. Disease Prevention, American Health Found tion, Valhalla, NY, 10595); Brunnemann, K. D.; Hoffman D. *In: Prevention and Detection of Cancer. Proceedings of t Third International Symposium on Detection and Preventi of Cancer Held by the International Study Group for the D tection and Prevention of Cancer in New York, April 26 - M 1, 1976.* International Study Group for the Detection a Prevention of Cancer. (New York, NY): Vol. 2(Part 1), 24 pp.; 1973-1992; 1978.

Techniques for analyzing polynuclear aromatic hydroca bons in tobacco smoke, air, and soil are reviewed, and the include various chromatographic and spectroscopic proc dures, gas chromatography/mass spectrometry, and isotop dilution. Detection data are tabulated, and some biologic data are also presented. (68 refs.)

78-6011 Carcinogenicity Testing of Chemicals with Pa ticular Reference to Organochlorine Pesticide (Eng) Reuber, M. D. (NCI Frederick Cancer Res. Cente

rederick, MD, 21501). *Sci Total Environ* 10(2): 105-115; 78.

he testing of chemicals, particularly organochlorine pesti-des, for carcinogenicity is reviewed. Classification of hepat- lesions in mice and rats, diagnostic criteria for malignant patic tumors in these animals, toxicity vs carcinogenicity, mparison of carcinomas and cirrhosis of the liver in ani-als and humans, and the significance of laboratory findings human health are covered. (66 refs.)

3-6012 **Scared of Cancer? Don't Blame Modern Agriculture.** (Eng) Grierson, W. (Univ. Florida, gricultural Res. and Education Center, Lake Alfred, FL). *arm Chemicals* 141(9): 69-76; 1978.

Whatever the causes of cancer, they long antecede the use modern agricultural chemicals or food additives. This atement is supported by the facts that all forms of cancer cept lung cancer are static or declining in the US, life ex-ctancy has increased over the past 50 yr, there is no docu-ented case of anyone in the US ever having been made sick a pesticide residue legally used, and there is evidence that DT is an anticarcinogen. (39 refs.)

8-6013 **Induced Plasma Cell Neoplasms.** (Pol) Salwa, J. (Zaklad Immunologii Nowotworow, Instytut nmunologii i Terapii Doswiadczalnej PAN, Czerska 12, 3-114 Wroclaw, Poland). *Postepy Hig Med Dosw* 31(6): 93-807; 1977.

he induction and antigenic properties of plasmacytomas are viewed. Plasmacytomas can be induced in mice by 6,10,14-tetramethylpentadecane, 2,6,10,14-tetramethyl-exadecane, and Abelson's virus. (51 refs.)

8-6014 **Health Problems Associated with Selected Petrochemicals: Benzene, Chlorinated Hydrocarbons, and Styrene-Butadiene Rubber.** (Eng) Lemen, R. A. Div. Surveillance, Hazard Evaluations and Field Studies, Natl. Inst. Occupational Safety and Health, U.S. Post Office nd Courthouse Building, Cincinnati, OH, 45202); Brown, . P.; Rinsky, R. A.; Young, R. J.; Meinhardt, T. J. *In: revention and Detection of Cancer. Proceedings of the Third nternational Symposium on Detection and Prevention of Can-er Held by the International Study Group for the Detection nd Prevention of Cancer in New York, April 26 - May 1, 1976.* nternational Study Group for the Detection and Prevention f Cancer. (New York, NY): Vol. 2(Part 1), 2404 pp.; 879-1891; 1978.

Hazards associated with occupational exposure to benzene, a recently recognized leukemogen; chlorinated hydrocarbons, known to be hepatotoxic and potentially carcinogenic and mutagenic to humans; and styrene-butadiene rubber, which has been connected with an increase in lymphatic and hematopoietic cancer, are reviewed. (66 refs.)

78-6015 **Structure and Carcinogenic Activity Relationships in the Benz(a)anthracene Series.** (Eng) Newman, M. S. (Chemistry Dept., Ohio State Univ., Columbus, OH). *In: Prevention and Detection of Cancer. Proceedings of the Third International Symposium on Detection and Prevention of Cancer Held by the International Study Group for the Detection and Prevention of Cancer in New York, April 26 - May 1, 1976.* International Study Group for the Detection and Prevention of Cancer. (New York, NY): Vol. 2(Part 1), 2404 pp.; 2093-2096; 1978.

The relationship between the structure and carcinogenicity of the 12 monomethylbenz(a)anthracenes and 9 of the possible nuclear monofluorinated-7-methylbenz(a)anthracenes is considered. It is hypothesized that two types of metabolism, a detoxification process and a carcinogenic process, are involved. Because 7-methylbenz(a)anthracene (7-MBA) is the most potent of the monomethyl derivatives, the 7-position is the spot at which detoxification is initiated. Because only 5-fluoro-7-methylbenz(a)anthracene is completely inactive, the 5-position is the spot at which the carcinogenic process is initiated. The fact that 1-, 2-, 3-, and 4-fluoro-7-methylbenz(a)anthracene are only slightly active indicates that the angular ring may also be involved in carcinogenesis. Steric effects are invoked to account for the moderate activity of 6- and 8-methylbenz(a)anthracene, for the fact that 7,12-dimethylbenz(a)anthracene is a more potent carcinogen than 7-MBA (the added methyl group at the 12-position produces strain due to overcrowding, which renders the molecule more reactive), and for the carcinogenicity of 12-methylbenz(a)anthracene, which does not contain a methyl group at the 6-, 7-, and 8-positions. The carcinogenicity of 7-MBA is caused by oxidative metabolism on the 7-methyl group, which results in the formation of an alkylating agent. The hypothesis is supported by metabolic studies using *Escherichia coli* and by carcinogenicity tests. (12 refs.)

78-6016 **Effects in Animals of Chronic Administration of Spironolactone--A Review.** (Eng) Lumb, G. (G. D. Searle & Co., 4901 Searle Pkwy., Skokie, IL, 60077); Newberne, P.; Rust. J. H.; Wagner, B. *J Environ Pathol Toxicol* 1(5): 641-660; 1978.

Studies of the effect of chronic administration of spironolactone to rats, dogs, and monkeys are reviewed. The animals were treated for up to 104 wk with daily dose levels (0-500 mg/kg) that were often higher than 100 times the recommended human dose. The pituitary, adrenals, and kidneys of

all animals showed no significant changes. Histological changes were noted in the rat liver, thyroid, and male internal genitalia. There were also alterations in monkey testes and male mammary glands. There was no evidence that spironolactone is tumorigenic or carcinogenic. (33 refs.)

78-6017 **The Crudeness of Coal Tar.** (Eng) Rasmussen, J. E. (Dept. Dermatology, State Univ. New York at Buffalo, Children's Hosp. Buffalo, Buffalo, NY). *Prog Dermatol* 12(5): 23-29; 1978.

The toxicology of coal tars is reviewed with emphasis on their carcinogenicity. Coal tars are known to contain four types of carcinogens: complete carcinogens, organ-specific carcinogens, tumor-promoting agents and cocarcinogens, and lymphoma-inducing naphthylenes. Industrial exposure to coal tar has been associated with an increased incidence of cutaneous malignancies, primarily on the sun-exposed areas of the skin but also on the scrotum. Larger studies are needed, however, to determine the risk factor for both external and internal cancers following coal tar exposure. (69 refs.)

78-6018 **Health Effects of Petroleum Extender Oils.** (Eng) Low, H. (Shell Oil Co., One Shell Plaza, Houston, TX, 77001). *J Elastomers Plast* 10(3): 229-240; 1978.

Experimental and epidemiological studies of the health effects of extender oils, high-boiling (315-538 C) fractions of petroleum that have been put through several refining steps, are reviewed. The skin and the pulmonary system are most likely to be exposed to these oils. Both skin painting and inhalation studies with various animal species have confirmed their carcinogenic potential. Epidemiological studies of workers exposed to oil, oil vapor, and oil mists in various occupational settings (ie, oil refineries and printing and metal working industries) have given ambiguous results. The health effects of exposure range from no apparent effect to excessive mortality. Significantly elevated mortality from cancer of the buccal cavity and pharynx was observed in one study of newspaper pressmen in the early and middle working years (20-54 yr old). Commercial pressmen showed little excess mortality from cancer of the buccal cavity, but they had a significant excess of cancer of the pancreas between ages 20 and 54 and rectal cancer after age 65. However, in another study involving 460 pressmen and 700 controls, no statistically significant increase in mortality rates was found. In a study of refinery workers, mortality from digestive cancer and all malignant neoplasms was higher in men with the lowest estimated exposure to atmospheric hydrocarbons, but respiratory cancer increased with increased exposure. (26 refs.)

78-6019 **Lung Cancer, Smoking, and Atmospheric F tion.** (Eng) Hansford-Miller, F. (No affili given). *Clean Air* 8(30): 27-31; 1978.

The premise is put forth that the increase in lung c during the last hundred years is not due primarily to ciga smoking but rather to the increase in CO_2 in the atmosp as a result of the industrial revolution and other assoc factors related to the earth's atmosphere. Combustion o sil fuels increases the amount of CO_2 discharged into th mosphere by 2 x 10^9 tons/yr. Up to half the amount of ca trapped in virgin grassland is lost upon cultivation. The b ing of lime in cement production is another major contrib of atmospheric CO_2. The current CO_2 level of 330 ppm i atmosphere is estimated to be increasing at a rate ppm/yr. Human lungs evolved at a constant CO_2 level, since 1850 this level has changed radically, as have the r of CO_2/O_2 and 14C/12C. The latter is due to the fact fossil fuels are essentially devoid of C14. Graphs show there is a very strong correlation between the incidenc lung cancer mortality and the combustion of fossil fuel is suggested that the inability of humans to adapt to t rapid changing atmospheric levels has resulted in cur lung cancer increases. (27 refs.)

78-6020 **The Role of Cytochrome P-450 in the Toxi of Xenobiotics.** (Eng) Lampe, J. (Central I Molecular Biology, Dept. Biocatalysis, Acad. Sciences GI Lindenberger Weg 70, DDR-115 Berlin, E. Germany); I schak, G. *Pharmazie* 33(7): 407-411; 1978.

Initiation of the formation of active metabolites from halo nated aliphatic and aromatic hydrocarbons, polycyclic a matic hydrocarbons, aflatoxins, nitrosamines, and arom amines by the cytochrome P-450-dependent enzyme syst is reviewed. (101 refs.)

78-6021 **Chapter XVII--Occupational Safety and Hea Administration, Department of Labor. P 1910 - Occupational Safety and Health Standards: Occu tional Exposure to Acrylonitrile (Vinyl Cyanide).** (Eng) Br kerhoff, G. (Office Complicance Programs, Rm. N-3112, O cupational Safety and Health Admin., Third St. a Constitution Ave., NW, Washington, DC, 20210). *Fede Register* 43(192): 45762-45819; 1978.

The final standard established by the Occupational Safe and Health Administration (OSHA) for exposure to acrylo trile (AN; vinyl cyanide), which becomes effective Novemb 2, 1978, is delineated in detail. Based on the results of expe mental studies that have shown excess tumor incidences AN-exposed animals and on indications of a cancer exce

nong workers exposed to AN, OSHA concluded that the mpound poses a carcinogenic risk to workers. In addition, N is mutagenic, an effect observed for other carcinogenic emicals. The permissible limit of occupational exposure to N was set at 2 ppm, as an 8-hr time-weighted av concentration with a ceiling level of 10 ppm for any 15-min period ring an 8-hr day. In addition, an action level of 1 ppm was tablished as an 8-hr time-weighted av. Provision is made r specific exemptions from the standard for the processing, ndling, and use of acrylic and modacrylic fibers, N-butadiene-styrene/styrene-AN resins, nitrile barrier resins, and nitrile rubbers when these materials are in the form finished polymers. The standard requires that employee posures be controlled by engineering and work practices, pplemented by respiratory and other protective equipment limited situations. It also requires the measurement of employee exposure, employee training, medical surveillance, nd recordkeeping. (no refs.)

8-6022 **The Health of Women in the Pharmaceutical and Chemical Industries.** (Eng) Cuthbert, J. W. May & Baker, Ltd., Dagenham Essex RM10 7XS, England). *Occup Med* 20(9): 601-604; 1978.

hanges in the pattern of women's employment, expansion f the chemical industry, and changes in legislation have increased the exposure of women to potential chemical mutagens, teratogens, and carcinogens, and advanced knowledge medicine and toxicology has heightened the awareness of is exposure. (19 refs.)

8-6023 **Pleural Reactions to Environmental Agents.** (Eng) Anderson, H. A. (Mount Sinai Sch. Medicine, City Univ. New York, New York, NY, 10029); Selikoff, J. *Fed Proc* 37(11): 2496-2500; 1978.

Radiographically evident pleural reactions to asbestos are described. Both pleural calcification (PC) and pleural thickening (PT) are seen in chest x-rays of asbestosis patients. Several studies have indicated that there is a long latent period before he appearance of pleural changes following occupational exposure to asbestos. Both PC and PT are uncommon with < 0 yr of exposure. PT and parenchymal fibrosis begin to be een after 10-11 yr, and PC becomes common after 30 yr. In study of 626 household contacts of workers employed in n asbestos factory, PT was the most prevalent radiographic bnormality (19%). PC was present in 8%, minimal parenchymal changes in 16%. These changes were significantly nore prevalent among the household contacts than among n age- and sex-matched control group from the same area vithout known asbestos exposure. The prevalence of abnormalities among household contacts increased with duration f the workers' employment. It should become evident in the ext 10 yr whether the levels of asbestos exposure in people iving in the vicinity of asbestos plants and in household contacts of workers were sufficient to cause serious disease. (30 refs.)

78-6024 **Role of Pineal Gland in Etiology and Treatment of Breast Cancer.** (Eng) Cohen, M. (Clinical Pharmacology Branch, NCI, NIH, Bethesda, MD, 20014); Lippman, M.; Chabner, B. *Lancet* 2(8094): 814-816; 1978.

The hypothesis is put forth that diminished pineal gland function and the subsequent inhibited secretion of melatonin may promote the development of human breast cancer (BC). BC has a known relationship with increased levels of secreted estrogen: 65% of BC cases have estrogen and progesterone receptors, and a relationship has been shown between BC and factors indicating a long exposure to estrogens, such as early menarche, late menopause, and few pregnancies. The pineal gland regulates gonadal function by the feedback inhibitory effect of melatonin on gonadal development and maturation; in fact, a specific melatonin receptor in peripheral gonadal tissue has recently been demonstrated. Therefore, it can be assumed that altered pineal function would release estrogen from the suppressive action of melatonin, and this excess estrogen could induce BC. Several lines of evidence have been developed to support this hypothesis. The rate of pineal calcification in populations and the incidence of BC are strongly correlated. Precocious sexual maturation is seen in children with pineal tumors. Female psychiatric populations, treated with serum-melatonin-raising phenothiazines, have a lower incidence of breast cancer. Finally, studies show that melatonin may influence the development of tumors in animals. If melatonin levels are found to be related to BC, this relationship would be of great value in screening for individuals at high risk. (35 refs.)

78-6025 **Radiation Leukemia in Humans.** (Fre) Tubiana, M. (Institut Gustave-Roussy, F-94800 Villejuif, France). *Schweiz Med Wochenschr* 108(41): 1563-1568; 1978.

The occurrence of leukemia in humans exposed to various doses and types of radiation is reviewed. The risk of leukemia from low doses of radiation such as those used in radiodiagnosis and from total body irradiation with doses exceeding 100 rads of x-rays or lower doses of neutrons was compared. Quantitative data on the incidence of leukemia in survivors of the atomic bomb explosions in Japan, in patients irradiated for ankylosing spondylitis or gynecological pathology, or in radiologists are reviewed. The dose-effect relationship between radiation and leukemia development appears to be curvilinear for large doses. The frequency of leukemia in subjects exposed to low doses of radiation, such as persons exposed occupationally or those living in the vicinity of a nuclear power station, is tabulated from literature studies. Linear extrapolation should not be used to evaluate the risk of small doses of radiation (doses in the range of a millirad). Studies of the effect of radiation in utero give conflicting results, although it appears that the small doses used for radiodiagnosis

do not present a risk. Literature reports on the increased rate of leukemia among patients treated with combination radiation and chemotherapy are reviewed. (17 refs.)

78-6026 **Hormonal Steroid Contraceptives: A Further Review of Adverse Reactions.** (Eng) McQueen, E. G. (Dept. Pharmacology, Univ. Otago Medical Sch., P.O. Box 913, Dunedin, New Zealand). *Drugs* 16(4): 322-357; 1978.

The adverse effects of oral contraceptives (OC) are reviewed extensively. Reports of benign hepatomas in women taking these drugs are numerous. A small number of these tumors have shown malignant change. A possible etiological association with steroid-induced hyperplasia of intracellular organelles is suggested. A positive association of sequential OC and endometrial adenocarcinoma and a negative association of OC and breast cancer are also suggested. (144 refs.)

78-6027 **Role of Exogenous Female Hormones in Altering the Risk of Benign and Malignant Neoplasms in Humans.** (Eng) Thomas, D. B. (Fred Hutchinson Cancer Res. Center, Seattle, WA, 98104). *Cancer Res* 38(11, part 2): 3991-4000; 1978.

Clinical and epidemiological evidence for the association of exogenous estrogens and the development of neoplasms of the breast, female genital system, or liver is reviewed. In utero exposure to diethylstilbestrol can cause clear cell adenomas of the vagina and cervix. Oral contraceptives very probably cause hepatic cell adenomas but reduce the risk of cystic disease and fibroadenomas of the breast. There is also strong evidence that various forms of estrogens given around the time of menopause increase the risk of endometrial carcinoma and that sequential oral contraceptives may also be a cause of this neoplasm. There is no consistent or conclusive evidence that any form of exogenous estrogens alters the risk of neoplasms of the breast or ovary or that oral contraceptives cause focal nodular hyperplasia of the liver or cervical neoplasia. However, recent studies suggest that the risk of these neoplasms may be increased, at least in some subgroups, by exposure to one or more forms of exogenous estrogens. (98 refs.)

78-6028 **Steroid Hormones and Endometrial Cancer.** (Eng) Siiteri, P. K. (Dept. Obstetrics, Gynecology and Reproductive Sciences, Univ. California at San Francisco Sch. Medicine, San Francisco, CA, 94143). *Cancer Res* 38(11, part 2): 4360-4366; 1978.

Factors that increase the risk of endometrial cancer, including obesity, nulliparity, late menopause, diabetes mellitus, hypertension, polycystic ovarian disease, hepatic disease, and ovarian tumors, are reviewed. Exogenous estrogens may play a causal role in the development of endometrial carcinoma in some individuals. The increased risk among estrogen u ranges from 3 to 8 and appears to be dose- and d tion-dependent. Estrogen users who develop cancer do exhibit any of the increased risk factors. Many of the co tions that place women at increased risk of endometrial cer (eg, obesity, hepatic disease) are associated with an ele ed production of estrone in peripheral (nonendocrine) tiss from circulating androstenedione. Neither the exact tis site nor mechanism of conversion has been established. fact that the constitutional features that have long been sociated with an increased risk of endometrial cancer are associated with increased peripheral estrogen productio a strong argument for the participation of endogenous es gens in the development of endometrial cancer. (74 refs

78-6029 **Cervical Cancer and Its Prophylaxis (Letter Editor).** (Dan) Clemmesen, J. (Cancerregister Denmark). *Ugeskr Laeg* 140(38): 2341-2343; 1978.

Epidemiological data on cervical cancer morbidity are viewed, and the etiology of this cancer is discussed. The m bidity rates per 100,000 persons, found in the 1950's, w 38.3 in Copenhagen, 17.2 in rural areas of Denmark, among Jewish women in New York, 17.1 among other whi in New York, and 32.8 among whites and 70.4 among blac in other parts of the US. The low incidence of cervical canc among Jewish women cannot be explained by circumcisio Epidemiological studies and various observations clea show that early sexual activity and promiscuity are predispo ing factors for cervical cancer. (15 refs.)

78-6030 **Identification of Tumor Susceptibility of I dividuals at High Risk for the Development Cancer.** (Eng) Rawson, R. W. (Univ. Texas System Canc Center, Houston, TX). *In: Prevention and Detection of Ca cer. Proceedings of the Third International Symposium on D tection and Prevention of Cancer Held by the Internation Study Group for the Detection and Prevention of Cancer New York, April 26 - May 1, 1976.* International Study Grou for the Detection and Prevention of Cancer. (New Yor NY): Vol. 2(Part 1), 2404 pp.; 1493-1512; 1978.

Factors that can identify high-cancer-risk individuals and/ populations are reviewed, and they include host or intrins factors (genetic, congenital, and immune deficiency diso ders, acquired nonneoplastic diseases, previous cancers), e vironmental factors (demographic, geographic, occupationa radiation, air pollution, viruses), and individual living pa terns (tobacco, alcohol, diet, drugs, sexual practices). (7 refs.)

78-6031 **An Epidemiological Perspective of the Biolog of Cancer.** (Eng) Doll, R. (Univ. Oxford, Ox ford, England). *Cancer Res* 38(11, part 1): 3573-3583; 1978

ıcer epidemiology data are reviewed to determine if they contribute to defining a mechanism of carcinogenesis. re is no evidence for genetic susceptibility to cancer as hole, but there are differences in susceptibility to individu- ypes of cancer. Epidemiological evidence suggests a possi- role for an infectious viral agent in African Burkitt's lym- ma, Hodgkin's disease, cervical cancer, and culosarcomas. The incidence of several types of cancer eases after 2 yr of treatment with immunosuppressive gs. The incidence of leukemia and lymphoreticular tu- s is much greater in patients with certain immunodefi- ıcy syndromes than in normal persons, but it is not clear ther the cancers are caused by the immunodeficiency or associated with it because of a common cause. Susceptibil- to radiation-induced cancer increases with age, perhaps result of a progressive breakdown in the efficiency of ınosurveillance with age. Studies on tobacco smoking lung cancer incidence indicate that the incidence in- ıses with duration of exposure and dose, independently ıge. The trend in smokers who stop smoking shows an ial fall in incidence followed by an increase, which keeps rate ahead of that in lifelong nonsmokers. The simplest lanation for these data is that cancer production is a mul- ıge process and that the various stages represent a series liscrete cellular changes that cumulatively result in the duction of a malignant clone. (45 refs.)

6032 **Cancer and the Environment.** (Eng) Thomas, H. F. (MRC Epidemiology Unit, Cardiff, Wales). *viron Health* 86(10): 232-233; 1978.

ne relationships between the environment and human can- s, 75% to 90% of which are estimated to be environmen- y caused, are considered. The cultural environment is the st important factor in cancer etiology, and it comprises oking, drinking, and eating habits. Agents in the general l occupational environments do not appear to be impor- t causes of cancer. In one report, it is argued that many he most potent carcinogens have not been in use for the bable latent interval (25-30 yr) before chemical cancers ome apparent. Likewise, cancers due to congenital, editary, iatrogenic, or viral causes appear to account for ery small proportion of the overall cancer incidence. The eraction of different agents, eg, asbestos and cigarettes, y increase the risk synergistically. (14 refs.)

-6033 **Some Current Concepts in Intestinal Bacteriology.** (Eng) Moore, W. E. (Anaerobe Lab., Vir- ia Polytechnic Inst. and State Univ., Blacksburg, VA, 061); Cato, E. P.; Holdeman, L. V. *Am J Clin Nutr* 31(10): 3-S42; 1978.

estinal bacteriology and its possible relevance to colon ıcer etiology are discussed. Recent studies indicate the pre- ıce in all human populations of intestinal bacteria that are capable of metabolizing sterols to carcinogens. However, comparisons of fecal flora in high- and low-colon cancer risk populations suggest that the relative proportions of certain bacterial species within a genera may be correlated with colon cancer incidence. In low-risk African and Japanese populations and high-risk North Americans, a positive correlation was noted between colon cancer and *Bacteroides vulgatus*, *Bacteroides distasonis*, and *Peptostreptococcus productus*. There was an inverse relationship between colon cancer and *Eubacterium aerofaciens* II, *Bacteriodes fragilis*, and *Escherichia coli*. Because flora of the transverse and descending colon and rectum are in the stationary growth phase, fecal bacteria adequately represent colonic flora. Bacterial response can be affected by epinephrine release during fear or anger reactions. Diet manipulation does not appreciably change intestinal flora, but high-fat diets may be involved in colon carcinogenesis by providing different substrates for bacterial action. Although technical problems make this type of study extremely difficult, future work must concern itself with the identification of carcinogens in the intestine, the bacteria responsible for their presence, and the factors that control their production. (59 refs.)

78-6034 **Common Intestinal Bacteria in Etiology of Colon Cancer (Meeting Abstract).** (Eng) Stortebecker, T. P. (Akerbyvagen 282, Taby, Stockholm, Sweden). *Acta Med Scand Suppl* (621): 46; 1978. (2 refs.)

78-6035 **Fecal Flora in Different Populations, with Special Reference to Diet.** (Eng) Finegold, S. M. (Infectious Disease Section, Wadsworth Veterans Admin. Hosp., Los Angeles, CA, 90073); Sutter, V. L. *Am J Clin Nutr* 31(10): S116-S122; 1978.

Studies of the fecal microbial flora of different populations are summarized. Two groups of Japanese-Americans, one on a Japanese diet and the other a western diet, exhibited significant differences in the occurrence of seven intestinal species or genera. Similarly, patients with multiple adenomatous polyposis differed significantly from controls in nine types of organisms. In both studies, however, there was little overlap in the species present in high- vs low-incidence colon cancer groups, so the differences could have been the result of chance variation. In neither study was there a significant difference in presence of *Clostridium paraputrificium* organisms. In a study of Seventh-Day Adventists (SDA's), *Clostridium septicum* and *Clostridium tertium* were significantly more common in non-SDA controls than in either vegetarian or nonvegetarian SDA's. Nonvegetarian SDA's, compared with other previously studied nonvegetarian groups, showed a much higher incidence of lactobacilli and a lower incidence of *Clostridium perfringens*. These and other studies demonstrated that fecal flora are remarkably constant, with only 21 organisms or groups of organisms differing in frequency between high- and low-incidence colon cancer populations.

These organisms should be studied for their ability to produce carcinogens or cocarcinogens from substrates such as bile acids. (21 refs)

78-6036 **Role of Diet and Nutrition in Cancer Cause, Prevention and Treatment.** (Eng) Gori, G. B. (Diet, Nutrition and Cancer Program, NCI, Building 31, Room 11A-03, Bethesda, MD, 20014). *Bull Cancer (Paris)* 65(2): 115-126; 1978.

The roles of diet and nutrition as etiologic factors in cancer incidence are reviewed. Epidemiologic evidence, including that obtained from studies of several migrant populations and ethnic groups, supports the hypothesis that different dietary constituents rather than other environmental contaminants are important in the cause of certain types of cancer. Fat consumption has been associated with some cancers, particularly bowel cancer. According to one theory, an excessive fat intake modifies the metabolism of cholesterol, bile acids, and neutral steroids in the intestine, as well as the metabolism and secretion of steroid hormones in the circulation. Bile acids secreted in the intestine could be degraded by intestinal bacteria to form carcinogens, or the altered metabolism of steroid hormones could impose unnatural burdens on cellular receptors of specific target tissues (uterus or breast). Animal studies strongly confirm the results of epidemiologic studies in humans. (74 refs)

78-6037 **Diet and Breast Cancer: A Review.** (Eng) Hankin, J. H. (Sch. Public Health, Univ. Hawaii, 1960 East-West Road, Honolulu, HI, 96822); Rawlings, V. *Am J Clin Nutr* 31(11): 2005-2016; 1978.

Human breast cancer (BC) is a multifactorial disease that is probably influenced by dietary intake. Studies of geographical variations in diet have shown that North America and northern Europe are high risk areas for BC, but countries in Africa and Asia are relatively low risk areas. The association of early menarche with higher risk and early first pregnancy with lower risk suggest that tumor initiation or inhibition may be determined in adolescence. Obesity may contribute to BC by influencing hormone synthesis and metabolism. Although dietary fat has been implicated in BC, dietary proteins, cholesterol, carbohydrates, and calories may also be involved. Studies of mammary tumor development in rodents indicate that tumorigenesis is associated with polyunsaturated rather than saturated fats; however, nutritional factors, including fat type, are more likely to act as promotors rather than initiators of tumorigenesis. Endocrinologic data indicate that women with a low ratio of estradiol to estrone and estriol are at high risk for BC. In rats, a high-fat diet increased serum prolactin levels and promoted mammary tumor development by 7,12-dimethylbenz(a)anthracene, but studies of prolactin levels in BC patients have yielded inconsistent results. The need for further research in all of these areas is emph (91 refs)

78-6038 **Workshop V--Fiber and Cancer: Summa Recommendations.** (Eng) Burkitt, D. P. (filiation given). *Am J Clin Nutr* 31(10): S213-S215; 1

Mechanisms whereby lack of fiber may promote colo cancer or whereby fiber may protect against this canc reviewed briefly. Applicable fecal parameters include n steroids, bile salts, and lipids; ammonia levels; pH; en activities; mutagenicity/carcinogenicity; transit time and water content; and microbial flora. (no refs)

78-6039 **Recent Progress in Dietary Fiber (Plant Human Nutrition.** (Eng) Spiller, G. A. (S Res., Palo Alto, CA); Shipley, E. A.; Blake, J. A. *CR Rev Food Sci Nutr* 10(1): 31-90; 1978.

Research performed since 1975 on the role of dietary (plantix) in human nutrition is reviewed. A hig low-plantix diet has been correlated with a high incide colorectal cancer. The significance of plantix may not an affector of transit time/constipation but rather as a d of colonic contents. However, other factors such as natu occurring antioxidants (vitamins E and C, selenium, e vitamin A may also play a key role in the etiology of col tal cancer. Many plantix polymers have a great capac interact with other dietary components. A study of 198 I colon cancer patients showed that they had a signific lower fiber consumption. Study of the etiology of colo cancer in Chile, where the incidence is very low, revealed the daily diet is a high-carbohydrate, low-protein, low- rated-fat one rich in plant fibers. One hypothesis adva is that plantix-associated factors, ie, lectin, may be inv in protecting against colon cancer. Several possible m anisms by which the body's response to undigested lecti the colon would protect against intestinal cancer are g Although many factors probably contribute to colon ca a higher intake of plantix and antioxidants may help to vent the disease. (161 refs)

78-6040 **Interaction of Dietary Fiber with Other Die Components: a Possible Factor in Certain cer Etiologies.** (Eng) Spiller, G. A. (Syntex Res., 3401 view Ave., Palo Alto, CA, 94304). *Am J Clin Nutr* 31 S231-S232; 1978.

The concept that dietary fiber, or "plantix" (ie, all polym plant materials that are indigestible by human digestive zymes) is an integral part of gastrointestinal physiol which cannot be studied purely on the basis of its pres or absence, is discussed. Plantix must be considered in te

f its interaction with other nutrients, and this pattern must e precisely identified. Plantix may affect the feces by altering t, general composition, or transit time. It may affect colonic icroflora directly, serving as a nutrient for certain organms, or it may carry other constituents to the colon that ould not arrive there otherwise. It may alter pH, the elimiation rate of microfloral metabolites or toxins, or dilute carinogens. Finally, it can alter the location and absorption rate f nutrients and the reabsorption of metabolites along the ntestine. All these factors suggest that a more complex eans of studying plantix is necessary, one that considers the nteractive facets of this dietary component. (3 refs)

78-6041 **The Relationship Between Bowel Cancer and Fiber Content in the Diet.** (Eng) Walker, A. R. Human Biochemistry Res. Unit, South African Inst. Medial Res., P.O. Box 1038, Johannesburg 2000, South Africa). *Am J Clin Nutr* 31(10): S248-S251; 1978.

A review of data on colon cancer in South African blacks SAB) indicates that the disease is very uncommon in this opulation. This rarity is not attributed to lack of adequate ase reporting since high and/or increased incidence rates ave been reported for cancers at certain other sites. There as been an increase in standard of living and urbanization f SAB; but in spite of the westernization in diet and way of ife, the risk of colon cancer remains the same. Since the ietary changes which accompany urbanization (decreased rude fiber in diet, longer fecal transit time, lower frequency f defecation and less feces voided per day) have been corelated with increases in colon cancer elsewhere, intrinsic facors seem to be protecting SAB. The existence of this protective factor is suggested by the unchanged incidence of ppendicitis, another disease which is usually seen to increase fter urbanization affects diet. Further research is needed on owel physiology fecal chemical composition, and enzymatic markers of intestinal microfloral activity in SAB. (19 refs)

78-6042 **Diet and Cell Growth Modulation by Ammonia.** (Eng) Visek, W. J. (Sch. Basic Science, Dept. Food Science, Univ. Illinois, Urbana, IL, 61801). *Am J Clin Nutr* 31(10): S216-S220; 1978.

The role of dietary fiber in the production and metabolism of ammonia by host cells, digestive enzymes, and gastrointestinal microflora is discussed. Fiber passes through the small intestine to the cecum and colon, where bacteria use it as an energy source for protein synthesis, in which the necessary nitrogen is supplied by ammonia. By facilitating the incorporation of ammonia into protein or its dilution, fiber reduces the harmful effects of ammonia on the gastrointestinal mucosa. Furthermore, fiber fermentation yields fatty acids that decrease colon pH and provide anions to trap free ammonia. Ammonia can induce cell proliferation, which enhances neoplastic transformation by increasing errors in DNA copying, increasing code breaking actions of mutagens present in subthreshold doses, or unmasking latent DNA changes caused by mutagens. Ammonia also alters cell life-span and metabolism, and enhances virus production. Although it does not transform cells per se, the incidence of polyps and cancers is highest in colonic areas with the highest ammonia concentrations. The role of fiber in removing free ammonia from the colon may explain the low incidence of colon cancer in populations with high-dietary fiber. (48 refs)

78-6043 **Colonic-Rectal Cancer: Fiber and Other Dietary Factors.** (Eng) Burkitt, D. P. (Unit Geographical Pathology, St. Thomas' Hosp., London SE1 7EH, England). *Am J Clin Nutr* 31(10): S58-S64; 1978.

The epidemiological evidence supporting the low fiber-high fat hypothesis for colon cancer etiology is comprehensively reviewed. Large bowel cancer bears a direct and constant relationship to economic development and westernization. Furthermore, within high incidence locales, there is an urban-rural correlation, with colon cancer being more prevalent in the urban areas. Chronological changes have also been documented; eg, the incidence rate in American blacks has increased significantly in the past generation. Groups that have immigrated from low to high incidence areas, notably the Japanese in Hawaii and California, show an increase in cancer incidence. Occurrence of other diseases, such as adenomatous polyps, diverticular disease, hiatus hernia and appendicitis, correlates with appearance of colon cancer, suggesting that all may result, at least to some degree, from common factors. Investigation has frequently centered on differences in fecal composition as a result of westernization and the accompanying decrease in dietary fiber and increase in fat intake. Hypotheses that have been put forth to explain how these dietary changes could result in cancer include decreased transit time, decreased dietary dilution, accumulation of toxins and carcinogens, or interactions between bacterial flora and dietary constituents. (52 refs)

78-6044 **Models Relating Ultraviolet Light and Non-melanoma Skin Cancer Incidence.** (Eng) Green, A. E. (ICAAS, Univ. Florida, Gainesville, FL, 32611); Hedinger, R. A. *Photochem Photobiol* 28(2): 283-291; 1978.

Various approaches used to relate UV light doses to nonmelanoma skin cancer (SC) incidence are reviewed. Three spectral response functions (DNA, Coblentz-Stair erythema response, and Robertson-Berger meter response) that have been used in epidemiological UV-SC studies are illustrated. If the DNA response function is the relevant one in SC, as seems most reasonable from a biophysical viewpoint, then a true dose-response relationship could depart significantly from an apparent relationship obtained by comparing meter readings with incidence data. Based on standard statistical

or epidemiological approaches, a double power law model seems to be as good a dose-response relationship as can be determined from Third National Cancer Survey data, which span a narrow range of annual doses. Various inductive approaches to dose-response relations are also reviewed. Despite the inconsistency of epidemiological data collected in different parts of the world, the data tend to favor multiple cause or age-exposure models over reciprocity, dose potency, and separable models. Both favored models are biophysically reasonable. Thus, the notion that there is more than one cause of SC is also suggested by evidence pointing to chemical carcinogens. The idea that age specific incidence rates of SC might depend on age and exposure is compatible with modern ideas on the degradation of immunological defenses. The application of the mathematical machinery of Reliability Theory to models relating UV light and nonmelanoma SC incidence is also illustrated. (54 refs)

78-6045 **Ultraviolet Light Mutagenesis in *Escherichia coli* (Meeting Abstract).** (Eng) Volkert, M. R. (Dept. Molecular Biology, Univ. California, Berkeley, CA, 94720). *Can J Genet Cytol* 20(3): 438; 1978. (no refs)

78-6046 **Solar Radiation and Skin Cancer.** (Nor) Fyrand, O. (Rikshospitalet, Hudavdelingen, Norway). *Tidsskr Nor Laegeforen* 98(24): 1139-1140; 1978.

In this literature review, the relationship between exposure to UV rays, natural or artificial, and precancerous changes in the skin and skin cancer is confirmed. The effect of the exposure is cumulative. A causal relationship between exposure to light and malignant skin melanoma is probable. (13 refs)

78-6047 **Comparison of Relative Risk from Radiation Exposure and Other Common Hazards.** (Eng) Kelsey, C. A. (Radiology Dept., Univ. New Mexico, Albuquerque, NM, 87131). *Health Phys* 35(2): 428-430; 1978.

Three comparisons are presented that have proven useful in putting effects from accidental or occupational exposure to radiation in perspective and in assisting radiation workers in evaluating the relative risks due to radiation exposure: (1) comparison of hazards from radiation exposure to hazards from various accidents in the US, (2) relative accident rates for various occupations in the US, and (3) comparison of the health hazards associated with cigarette smoking and radiation. Results are reported in terms of hazard/rem (roentgen equivalent man) exposure, assuming that there is no recovery from radiation injury and that the effect of 1 rem is the same whether delivered over periods of 1 mo, 1 yr, or 5 yr. Deaths per yr per million persons are 9 for each rem of radiation compared to 4,780 for cardiovascular disease. Among 15 occupations, radiation workers have the lowest risk of job-ed accidental death (0.02 relative death rate) and miner highest (6.2). The life shortening effect of smoking one rette is equivalent to exposure to 2.5 mm radiation. (7

78-6048 **A Stochastic Model of Carcinogenesis I porating Certain Observations from Cher and Radiation Dose-Response Data.** (Eng) Brodsky, A. fice of Standards Development, U.S. Nuclear Regula Commission, Washington, DC, 20555). *Health Phys* 3 421-428; 1978.

A stochastic model of carcinogenesis that incorpo phenomena regarding the sequential interactions of c cinogens is presented. There is preliminary evidence from mal experiments that this model is consistent with obse quantitative dose-response relationships. An example i dose-response relationships for radiation carcinogenesis (tumors in mice implanted with Ru^{106} pellets or administ Ce^{144} intratracheally). The two-step sequential stoch model may provide an alternative model to the log-no model for interpreting a broad range of radiobiological toxicological effects. (9 refs)

78-6049 **The Combined Effects of Ionizing Radia and Smoking in the Development of Bronc Carcinoma.** (Ger) Schuttmann, W. (Hauptabteilung St lenschutzmedizin, Staatlichen Amtes fur Atomsicherheit Strahlenschutz der DDR, Waldowallee 117, DDR-1157 lin, E. Germany). *Z Erkr Atmungsorgane* 150(3): 243- 1978.

Evidence that smoking increases the probability of respir ry tract cancer developing in individuals previously expo to ionizing radiation is reviewed. Uranium miners smoked had a respiratory tract cancer rate of 17/10,000 son-yr, but nonsmoking miners had a rate of only 1.7/10, person-yr. Miners who smoked more than one pack of c rettes/day had a significantly shorter av tumor-latency p od than nonsmokers. This type of effect is typical of tha a tumor promoter. The finding that the same proportion small cell and epidermoid lung cancers occurs in smoking nonsmoking uranium miners also suggests that smoking a promoting or cocarcinogenic effect. These findings h significance for the nonmining population. The av ann radiation dose to the lungs from natural sources (ie, burni of fossil fuels, presence of ^{210}Pb and ^{210}Po in tobacco smo is 250.5 millirems (rem = roentgen-equivalent-man) for general population. Thus, every smoker suffers the combin effects of radiation and smoking. (15 refs)

78-6050 **Can Animal and In Vitro Studies Give Ne Relevant Answers to Questions Concerni**

ammographic Screening for Human Breast Cancer? (Eng) thlefsen, L. A. (Section Radiation and Tumor Biology, pt. Radiology, Univ. Utah Medical Center, Salt Lake City, T, 84132); Brown, J. M.; Carrano, A. V.; Nandi, S. *J Natl ncer Inst* 61(6): 1537-1545; 1978.

is report of an ad hoc committee appointed by the NCI east Cancer Task Force reviews current arguments surnding the role of mammography in breast cancer develop-nt and recommends directions for future research using imal or in vitro models. Human carcinogenesis studies ve shown that the risk of breast cancer from ionizing radian is not diminished by dose fractionation and is highly age pendent, resulting in an excess risk of 7.5 cases/10^6 women/ /rad for women <35. In rats, fractionation of a 500 R se did not change the overall incidence of mammary tuors, but it increased adenocarcinoma incidence and deeased fibroadenoma incidence. Hormonal factors modify diation-induced mammary cancer in rats, and postpubertal imals are at higher risk than prepubertal animals. On the sis of current knowledge of cell transformation mechisms and the results of present study protocols, two specific eas of future research are suggested: the specific effects of diation dose fractionation of the efficiency of cell transforation, and the relationship between DNA repair processes d transformation. The mammary fat pad transplantation chniques and established in vitro cellular transformation stems is suggested. No further animal studies aimed at uantifying the tumor risk per rad should be initiated at this me. (58 refs)

8-6051 **Iatrogenic Carcinogenesis.** (Hun) Schuler, D. (II. Gyermekklinika, Semmelweis Orvostudomanyi Egyetem, Budapest, Hungary). *Orv Hetil* 119(37): 239-2243; 1978.

onizing radiation and drugs with carcinogenic, cocarcinoenic or immunosuppressive effects lead to iatrogenic carinogenesis. These drugs include cyclophosphamide, busulan, chlorambucil, melphalan, 6-azauridine, chlornaphazin, rsenicals, hydantoin derivatives, phenacetin, diethylstilbetrol, and 18-methylnorethisterone. (92 refs)

8-6052 **Multiple Pathways of DNA Repair in Bacteria and Their Roles in Mutagenesis.** (Eng) Smith, C. C. (Dept. Radiology, Stanford Univ. Sch. Medicine, Stanord, CA, 94305). *Photochem Photobiol* 28(2): 121-129; 1978.

Photoreactivation, excision repair, and postreplication repair f DNA in bacteria are reviewed in relation to mutagenesis, vhich appears to be the result of error-prone DNA repair. There is growing evidence that carcinogenesis is also the reult of error-prone DNA repair. One pathway of postreplicaion repair has been shown to be blocked by postradiation reatment with the protein synthesis inhibitor chloramphenicol (CAP), suggesting that protein synthesis is required after UV irradiation before this pathway can function. This pathway requires functional *uvrD*, *recB*, and *lexA* genes. UV-induced mutagenesis is blocked by postradiation treatment with CAP, suggesting that the *uvrD*, *lexA*, and *recB* gene products are involved in mutagenic repair. The fact that UV-induced mutations are not observed in *lexA* strains seems to support the idea that the CAP-inhibitable pathway is the mutagenic pathway. An area of mutagenesis research that is currently receiving considerable attention is based on the concept that error-prone (mutagenic) repair is due to a new repair function (the so-called SOS repair system) that is induced by damage produced in DNA. Since UV-induced mutagenesis is prevented by a short postradiation treatment with CAP, postradiation protein synthesis is apparently required for the expression of UV-induced mutations. The *recA* and *lexA* strains are not UV mutable; therefore, *recA*+ *lexA*+ functions are probably essential for expressing this inducible error-prone repair function. (75 refs)

78-6053 **Evaluation of DNA Damage and Repair in Mammalian Cells Exposed to Chemical Carcinogens. Methods Potentially Useful as Short Term Prescreening Tests.** (Eng) Brambilla, G. (Dept. Pharmacology, Univ. Genoa, Genoa, Italy); Cavanna, M.; Parodi, S. *Pharmacol Res Commun* 10(8): 693-717; 1978.

Autoradiographic techniques for detecting unscheduled incorporation of labeled nucleotides into mammalian DNA and techniques for detecting single-strand DNA breaks in alkali are discussed in relation to their ability to predict the oncogenic potential of chemical agents. Although potentially good indicators of carcinogenic risks in humans, carcinogenicity tests in rodents present problems related to possible species differences in the metabolic activation of procarcinogens. This method is also time-consuming and expensive. Mutagenicity tests such as the Ames assay provide rapid information, and a short-term test based on DNA damage-repair in mammalian cells would be a useful complementary test. Of the short-term tests, the evaluation of DNA damage in vivo by the alkaline elution technique may prove to be the method of choice. To confirm its predictive value, the test should be extended to the evaluation of several hundred carcinogenic and noncarcinogenic compounds of different chemical structures. (122 refs)

78-6054 **A Re-evaluation of Evidence for Carcinogen-induced DNA "Repair" Synthesis.** (Eng) Melzer, M. S. (2550 Kemper Road, Shaker Heights, OH, 44120). *Chem Biol Interact* 22(2/3): 359-363; 1978.

The argument that carcinogenesis involves primary attack on nuclear DNA in the crucial reaction of the transforming process is based mainly on studies concerning 'repair' or unscheduled DNA synthesis. If it can be demonstrated that

upon treatment with a carcinogen, there is additional DNA synthesis (increased incorporation of labeled thymidine into DNA) of a nonreplicative type, this would indicate that a lesion has been introduced into the DNA that was being repaired, suggesting direct carcinogen-DNA interaction as the crucial step in carcinogenesis. This study evaluates the evidence for such carcinogen-induced repair synthesis and suggests that some of it is distinctly flawed. In fact, some of the evidence could just as well be interpreted as evidence for carcinogen-induced replicative DNA synthesis, which would point up the fact that carcinogens, in their initial effect on target cells, induce increases in (or even initiation of) new replicative DNA synthesis and/or new mitosis. It is hoped that the points raised will stimulate further thinking among carcinogenesis researchers about possible alternative mechanisms of initial cellular attack by chemical carcinogens. (27 refs)

78-6055 **DNA Repair and Mutagenesis in Mammalian Cells.** (Eng) Hart, R. W. (Dept. Radiology, Ohio State Univ. Sch. Medicine, Columbus, OH, 43210); Hall, K. Y.; Daniel, F. B. *Photochem Photobiol* 28(2): 131-155; 1978.

Mammalian cell DNA repair is reviewed in relation to mutagenesis and carcinogenesis. Although DNA damage leads to measurable mutations in mammalian cells, the means by which this damage results in an inheritable change in base sequencing is not known. Depending on the type of insult and its location within the DNA, inheritable errors could arise during excision repair, DNA replication, or postreplication repair. Among the clinical syndromes associated with mutagenesis that have been studied most extensively are xeroderma pigmentosum (XP), dyskeratosis congenita, Fanconi's anemia, ataxia telangiectasia, and Werners, Bloom's, Chidiak-Higoski, Hutchinson-Gilford, and Down's syndromes, all of which have a genetic predisposition to cancer and/or other specific syndrome anomalies. XP is characterized by hypersensitivity of the skin to solar radiation, a high incidence of multiple carcinomas, and deficiencies in DNA repair. The predisposition to cancer among XP patients is inversely proportional to their ability to repair UV radiation- and acetoxyacetylaminofluorene-induced damage. An explanation for the high frequency of mutation in XP variants, which are slow in postreplication repair but have normal excision repair, involves the possibility that the DNA polymerase III-like complex is altered, leading to the observed mutation frequencies. In bacterial systems, mutations in the gene for DNA polymerase III can lead to enhancement of spontaneous mutations in vivo. (326 refs)

78-6056 **Glycopeptide Changes and Malignant Transformation: A Possible Role for Carbohydrate in Malignant Behavior.** (Eng) Warren, L. (Wistar Inst. Anatomy and Biology, 36th St. at Spruce, Philadelphia, PA, 19104); Buck, C. A.; Tuszynski, G. P. *Biochim Biophy* 516(1): 97-127; 1978.

Studies comparing glycopeptides (GP) isolated from c and transformed animal cells are reviewed. Sephadex chromatography of Pronase-treated GP yields, among fractions, groups A and B GP, which elute at mol w approx 4,600 and 3,700, respectively; upon removal of acid, these peptides are reduced to a common size bu a common substructure. After Pronase digestion, g proteins producing groups A and B GP have been foun sociated with nuclei, mitochondria, lysozomes and endo mic reticulum. Group A material is increased in malig cells regardless of transforming agent or species of origin it is strongly growth-dependent. Its presence has been related with tumorigenesis and noted both in vivo a vitro. The total number of GP may be constant in no and transformed cells, and as the number of group A increases, the number of group B GP decreases. Studies made of GP derived from individual glycoproteins of id cal mol wt and isoelectric point from control and transfo cells. Among 24 different pairs of homologous glycoprot 20 differences of varying degrees of severity were noted. parently, the gross increase of group A GP seen upon phadex chromatography is the cumulative result of se changes in the carbohydrate components of many gl proteins in crude fractions. It is hypothesized that t changes, particularly in the cell membrane, where m glycoprotein activity is found, do not endanger premalig cells but alter their relationships with external factors influences. This alteration could then lead to malig change, perhaps by removing the cells' sensitivity to t external controlling factors. (188 refs)

78-6057 **High Molecular Weight, Cell Surface-asso ed Glycoprotein (Fibronectin) Lost in Ma nant Transformation.** (Eng) Vaheri, A. (Dept. Virol Univ. Helsinki, 00290 Helsinki 29, Finland); Mosher, D *Biochim Biophys Acta* 516(1): 1-25; 1978.

The literature on fibronectin (FBN), a polymorphic gly protein found in blood and tissues of vertebrates and in tures of adherent vertebrate cells, is reviewed, and the sig cance of its loss from surfaces of transformed cells in v and the relationship of FBN to the biology of cancer cell vivo are discussed. Two forms of FBN have been identif a high-mol wt, cell-surface-associated, transformation-se tive form (I) and a high-mol-wt circulating form (II). Fo I is decreased consistently in cells transformed by virus including virus mutants temperature-sensitive for transf mation. Cells from human glioblastomas, fibrosarcom rhabdomyosarcomas, and osteosarcomas produce FBN have little form I FBN. Compared with normal parental ce form I is also decreased in spontaneously and chemica transformed rodent cells. Among adenovirus-transformed embryo cells, there is a close correlation between a decre in cells positive for FBN immunofluorescence at cell-cell c

ct and an increase in tumorigenicity in syngeneic rats and ıde mice. Although, there are exceptions, the conclusion at malignant cells may have a normal complement of surce-associated FBN seems premature when these exceptions e compared with well-characterized virally transformed or mor-derived cells of genetically stable species. Transformaon appears to be associated with alterations of FBN, sulfat- glycosaminoglycans, and collagen, but it is not known how ese components interact in vivo and in vitro. A decreased sociation to matrix components by malignant cells may be ucial to unregulated growth. It is suggested that transrmed cells have defective interactions and associations with atrix elements and thus are free to divide and move. Little known of the role of form II FBN in neoplasia. Changes this form are not common in patients with malignancies. 92 refs)

3-6058 **Stress and Cancer: Fresh Perspectives.** (Eng) Riley, V. (Pacific Northwest Res. Foundation, eattle, WA, 98104). *In: Prevention and Detection of Cancer. roceedings of the Third International Symposium on Detecon and Prevention of Cancer Held by the International Study roup for the Detection and Prevention of Cancer in New ork, April 26 - May 1, 1976.* International Study Group for ıe Detection and Prevention of Cancer. (New York, NY): ol. 2(Part 1), 2404 pp.; 1769-1776; 1978.

tudies of the relationship between stress and cancer are reiewed. According to epidemiological studies, religious roups such as Mormons and Seventh-Day Adventists have reduced incidence of cancer even at anatomical sites not enerally associated with the effects of smoking or alcohol onsumption. This suggests the beneficial influences of a less tressful life-style upon pathological processes. Psychosocial creening questionnaires have been employed in an effort to orrelate personality traits and cancer risk. A multihormonal pproach for deciphering the effects of stress has led to the uantification and integration of the behavior of a broad specrum of interrelated hormones associated with stressful vents. The known interference of stress with immunocompeence appears to be the most promising rationale for the induction of disease by acute, chronic, or intermittent stress. Certain varieties of stress, however, suppress specific neoplasic processes rather than enhancing them. There is no explaıation for this paradox. The enhancement of tumor growth or of tumor incidence by stress probably can only be observed in experimental circumstances in which the host exerts a total or partial controlling influence on the establishment or growth rate of the tumor. It is the disruption of such host control that permits stress to enhance pathological processes. (17 refs)

78-6059 **Etiology of Cancer as Studied in the Platyfish-Swordtail System.** (Eng) Anders, A. (Genetisches Institut der Justus-Liebig-Universitat Giessen, Heinrich-Buff-Ring 58-62, D-6300 Giessen, W. Germany); Anders, F. *Biochim Biophys Acta* 516(1): 61-95; 1978.

Research in cancer etiology utilizing the platyfish-swordtail (Xiphophorine fish) tumor system is reviewed. Although inbreeding of wild-type populations produces only normal offspring, interspecific and interpopulational crossings produce progeny that spontaneously develop various neoplasms, including melanomas, pterinophoromas, neuroblastomas, thyroid carcinomas, kidney carcinomas, and reticulosarcomas. Genetic information coding for neoplastic transformation is represented by a "tumor gene" (Tu), which may be present in several copies on different chromosomes, including one copy on the terminal portion of the sex chromosome. Tu is normally repressed by cell-type-specific systems of regulating genes. Four types of neoplasm-triggering mechanisms have been recognized in this model, all mediated by Tu. These include altered cell differentiation, somatic mutation, germ line mutation, and hybrid crossings. However, neoplasms are usually initiated by a combination of tumor-inducing methods, and the ultimate type of cancer is always determined by the last step in the multistep process. The different cell stages of transformation in the melanophore system to melanoma have been well-characterized. Certain melanomas are preferentially located in certain compartments of the fish body, and 13 different genes governing 13 different compartments of melanoma expression are linked to the Tu. Likewise, the malignancy and benignancy of melanoma are apparently regulated by presence of the single gene R-Diff. Experiments on neoplasia etiology in this tumor system support generally accepted concepts for the origin of cancer and disclose relationships among the different concepts. (177 refs)

78-6060 **Specificity of Arrest, Survival, and Growth of Selected Metastatic Variant Cell Lines.** (Eng) Nicolson, G. L. (Dept. Developmental and Cell Biology, Univ. California, Irvine, CA, 92717); Brunson, K. W.; Fidler, I. J. *Cancer Res* 38(11, part 2): 4105-4111; 1978.

Animal tumor models for blood-borne metastasis that were developed by in vitro cloning or in vivo selection of malignant tumor cell populations to obtain organ-preferring variant tumor cell lines with altered arrest, survival, invasion, and growth properties are reviewed. Selection and some tumor cell characteristics of lung-, brain-, and ovary-colonizing metastatic B16 melanoma variants, liver-colonizing RAW117 lymphosarcoma variants, and lung-colonizing sarcoma variants are discussed. Cloning and fluctuation tests with the B16-F1 melanoma cell line and with a vasoformative sarcoma, MSV3T3-LN, demonstrated the presence of populations of high and low metastatic potential before in vivo selection, suggesting that each in vivo selection results in enrichment of more metastatic cells in each subsequent cell line established in culture. Organ preference in arrest and colonization may be explained by adhesive interactions of circulating tumor cells with noncirculating host cells in the target organ or by adhesive interactions leading to arrest in the mi-

crocirculation at specific locations. Tumor cell invasion appears to occur by a combination of mechanical and enzymatic mechanisms. In addition to unique tumor cell characteristics, host properties such as immune response can influence metastasis. Therefore, both tumor cell and host properties probably determine whether metastasis occurs in each tumor-host system. (48 refs)

78-6061 **Cell Membrane Ionic Permeability, Calcium Ion, Mitochondria, and Carcinogenesis.** (Eng) Anghileri, L. J. (Department de Protection, Boite Postale No. 6, 92260 Fontenay-Aux-Roses, France). *Arch Geschwulstforsch* 48(6): 497-503; 1978.

Cumulative evidence in support of a hypothesis of carcinogenesis at the cellular level is reviewed. The hypothesis states that a carcinogen, chemical or viral, alters cell membrane permeability, which upsets the normal intracellular ionic composition of the cytoplasm and allows excess calcium ions to flow into the cell. Calcium is sequestered in the mitochondria, resulting in damage to its oxidative phosphorylation mechanism and also to its genetic component. Therefore, the cell will shift toward glycolytic means of energy production. Moreover, if released from damaged mitochondria into the cytoplasm, mitochondrial DNA may become incorporated into the nuclear genome and may induce malignant transformation. The role of mitochondrial DNA in the specification of membrane characteristics is also important. Damage to this function may lead to the loss of growth inhibition and communications with neighboring cells and effectors that is noted in transformed cells. (55 refs)

78-6062 **Pathogenesis of Attic Cholesteatomas.** (Eng) Beales, P. (Royal Infirmary, Doncaster, England). *J R Soc Med* 71(10): 707-708; 1978.

The congenital, migration, and metaplasia theories of the pathogenesis of attic cholesteatomas (AC) are reviewed. Although the migration theory is the one most commonly accepted, the evidence of contact inhibition of stratified squamous epithelium and the absence of documentation of the evolution of AC from a preexisting perforation or from marginal perforations argue against this theory. The exact mechanism of AC formation is not known. (11 refs)

78-6063 **Small Cell Carcinoma of the Lung: Cellular Origin and Relationship to Other Neoplasms.** (Eng) Tischler, A. S. (Dept. Pathology, Tufts Univ. Sch. Medicine, 126 Harrison Ave., Boston, MA, 02111). *Semin Oncol* 5(3): 244-252; 1978.

The origin and behavior of small cell carcinoma of the lung are considered in relation to its similarity to APUD (amine precursor uptake and decarboxylation) cells. Cells from s cell carcinomas of the lung and from the more benign pu nary carcinoid tumors contain secretory granules tha morphologically and, to some extent, cytochemically sir to those in normal pulmonary APUD cells. Both tumors produce amine and peptide hormones. Carcinoids have observed in association with increased numbers of AP cells that might represent hyperplasia or neoplasia in situ such observations have not been documented for small carcinomas. Although small cell carcinomas have m similarities to carcinoid tumors and to normal pulmo APUD cells, it cannot be stated that they arise from specific cell type. Because the embryologic lineages of nor pulmonary APUD cells have not yet been determined certainty, small cell carcinomas would have an unclear or even if they had been observed histologically to arise f such cells. Some tumors that currently are classified as sm cell carcinomas probably do not have APUD cell charact tics, but others appear to have both APUD and non-AP features. A subclassification of small cell carcinomas ba on a combination of physiological and morphological tures might prove of prognostic and therapeutic value. refs)

78-6064 **Nasopharyngeal Carcinoma. Aetiological pects and Electronmicroscopic Observatio** (Eng) Prasad, U. (Dept. Otolaryngology, Univ. Mala Kuala Lumpur, Malaya). *J R Coll Surg Edinb* 23(199-207; 1978.

Current knowledge of the etiology of nasopharyngeal c cinoma (NPC) is reviewed, and the results of an electr microscope study of 60 cases are presented. The study su ports the view that NPC originates from squamous epithe cells, and it indicates that, in addition to genetic factors, en ronmental factors play a significant role in the etiology NPC. (48 refs)

78-6065 **Metastatic Potential of Malignant Tumo** (Eng) Carter, R. L. (Inst. Cancer Res., Sutto England). *Invest Cell Pathol* 1(3): 275-286; 1978.

The metastatic potential (MP) of malignant tumors and co tributing factors are reviewed based on clinical and expe mental observations. Morphological factors include tum site, size, and histology and the pattern of local tumor sprea This information can be supplemented by techniques such immunoperoxidase staining to determine MP. Howeve more functional, nonmorphological features of the prima tumor are likely to be of greater importance. These featur are the functional heterogeneity of tumor cells with respe to MP; the elaboration of certain tumor-associated produc that may potentiate tumor spread; and immunological facto in the form of local host cell infiltrates in and around primar tumors. Tumor-associated products include substances tha

ginate largely or wholly from tumor cells and host cells. nor-specific antigens, ectopically produced hormones, l tumor angiogenesis factor may thus be contrasted with staglandins and collagenases. Irrespective of their cellular gin, however, both types of products contribute to MP. us, some host factors may act as determinants of metasta- a view compatible with evidence that shows that host cells netimes make up a far larger proportion of tumor popula- ns than would be expected from conventional morphology. s concluded that the MP of tumors cannot be assessed in ns of conventional tumor pathology alone. (122 refs)

6066 **Constitutional Factors and Endometrial Carcinoma.** (Eng) Lynch, H. T. (Dept. Preventive edicine, Creighton Univ., Omaha, NB); Lynch, P. M. *In: evention and Detection of Cancer. Proceedings of the Third ernational Symposium on Detection and Prevention of Can- Held by the International Study Group for the Detection d Prevention of Cancer in New York, April 26 - May 1, 1976.* ernational Study Group for the Detection and Prevention Cancer. (New York, NY): Vol. 2(Part 1), 2404 pp.; 05-2117; 1978.

veral etiological factors in endometrial carcinoma (EMC) re identified by a review of the medical records of 154 MC patients treated at one hospital from 1946 to 1965. The ost common finding was obesity (123/154), which was mas- e in some patients. Other constitutional factors included pertension (100/154) and diabetes mellitus (66/154). The ad of obesity, hypertension, and diabetes was seen in 46 omen. A review of the literature indicated that nulliparity d late natural menopause are also risk factors for EMC. n autopsy series of 30 patients who died from EMC revealed gnificant aberrations in pituitary, ovarian, pancreatic, and renal histology. Initial studies have not revealed any sy- rgistic interaction between constitutional factors and ex- genous estrogen. Multiple genotypes have been postulated explain the occurrence of EMC in several familial cancer ndromes. It is suggested that the inherited gene(s) defect certain instances of familial EMC may initially express self in the endocrine system, possibly involving the pitui- ry-adrenal axes. Speculation that the adrenals might be the te of the inherited endocrine lesion is supported by statisti- l indications that adrenal estrogen production may have a eritable basis. (32 refs)

8-6067 **An Overview of Hormone-associated Cancers.** (Eng) Miller, A. B. (NCIC-Epidemiology Unit, aculty Medicine, Univ. Toronto, Toronto, Ontario M5S A8, Canada). *Cancer Res* 38(11, part 2): 3985-3990; 1978.

ata on the etiology of hormone-associated cancers, particu- rly breast cancer, are reviewed. Although many breast can- er risk factors point to the relevance of hormonal factors, ne findings are not uniform. If age at first pregnancy is the prime epidemiological indicator of some largely internally influenced hormonal mechanism and if the risk ratio of approx 1.7 from the literature is appropriate, then the attributable risk (AR) for this factor is approx 25%. Family history of breast disease, with a risk ratio of 2.4, results in an AR of 20%. Finally, total fat intake, by a weighted av over pre- and postmenopausal women, results in an AR of 27%. The AR's for age at first pregnancy, which may be overestimated, and total fat intake, which may be underestimated are the most doubtful. There also may be an interaction between the two, and neither may adequately reflect the true risk factor. However, evidence points to the importance of dietary factors, and one study appears to confirm an association with high total fat intake. Dietary factors, although possibly mediated by a hormonal mechanism, may be found to play a major role in the etiology of breast cancer. Studies of endometrial and ovarian cancer also show the importance of hormonally associated factors, although not always the same way as for breast cancer. For both these cancers and for cancer of the prostate, dietary factors may also be relevant in their etiology. (47 refs)

78-6068 **Genetic Factors in the Etiology of Breast Cancer.** (Fre) Sancho-Garnier, H. (Departement de Statistique medicale, Institut Gustave-Roussy, 16 bis, avenue P.-V.-Couturier, F 94800 Villejuif, France); Henry-Amar, M.; Le, M. *Bull Cancer (Paris)* 65(2): 127-130; 1978.

Literature studies on the relationship of genetic factors to the development of breast cancer are reviewed. A higher risk is present for women with mothers or sisters with premenopausal breast cancer. Only a few studies have evaluated the incidence of breast cancer in twins but a concordance of 0.28 has been found for monozygotic twins vs 0.12 for dizygotic twins. The incidence of breast cancer in various ethnic groups changes upon migration, which indicates that environmental factors are involved. Attempts have been made to identify specific markers such as blood group, human leukocyte antigens (HLA), or fingerprints that may be associated with high-risk populations. An increased incidence has been found for young patients with type O blood and older patients with type A. The HLA haplotypes 2-12 and 10 have been found in families with tendency to develop breast cancer. One unconfirmed study relates cancer incidence to fingerprint characteristics. Apparently, families with breast cancer are more likely to be carriers of mammary tumor virus. As for many types of cancer, the development of breast cancer is probably due to a multigenetic transmission of susceptibility and to the action of environmental factors. (27 refs)

78-6069 **Tumors of Dysgenetic Gonads in Females with Y Chromosome.** (Pol) Boczkowski, K. (Samodzielna Pracownia Genetyki, Instytut Ginekologii i Poloznict-

wa AM, pl. Starynkiewicza 1, 02-015 Warsaw, Poland). *Postepy Hig Med Dosw* 32(3): 381-390; 1978.

Studies of the frequency, genetic basis, and origin of tumors of dysgenetic gonads in women with Y chromosomes are reviewed. Dysgerminoma of the left ovary was diagnosed in a 21-yr-old eunuchoid woman with a 46,XY karyotype. (31 refs)

78-6070 **Chromosomes and Cancer.** (Eng) Brown, J. K. (Radiation Biology Section, Australian Atomic Energy Commission, Private Mail Bag, Sutherland, New South Wales 2232, Australia). *Cancer Forum* 14: 97-100; 1978.

The origin of cancer may be due to a genetically unbalanced chromosome complement that predisposes a cell to malignant transformation. On the other hand, chromosome anomalies may be of a secondary nature, merely accompanying the more significant changes. Many, but not all, cancer cells have chromosome abnormalities. Clonal evolution is common in neoplasms, particularly leukemias. At present, only a few specific chromosome abnormalities characteristic of particular neoplasms have been found. (no refs)

78-6071 **Hereditary Retinoblastoma: Delayed Mutation or Host Resistance?** (Eng) Matsunaga, E. (Dept. Human Genetics, Natl. Inst. Genetics, 411 Mishima, Shizuoka-Ken, Japan). *Am J Hum Genet* 30(4): 406-424; 1978.

A review of 261 pedigrees with 2 or more cases of retinoblastoma taken from 11 different sources indicates that host resistance explains the variation in the expression of the retinoblastoma locus and that there is little need to postulate delayed mutation. Both penetrance and expressivity in the gene carrier can be defined as a variable determined by genetic and environmental factors, not by Poisson distribution of tumors formed. Of individuals who receive a new mutation from a healthy parent, approx 13% do not manifest retinoblastoma; the heritability of the host resistance is estimated at about 90%. Significant associations of human WBC antigens with retinoblastoma have been reported, and the cell-mediated immune response is thought to play a role in host resistance. The host resistance model suggests that nonhereditary retinoblastoma, due to somatic mutations, occurs in the most susceptible group of the general population, whereas unaffected carriers, including spontaneously regressed cases, are the most resistant group. Therefore, a genetic marker correlated with host resistance to retinoblastoma would be found with decreasing frequency in unaffected carriers, hereditary unilateral cases, the general population, and bilateral and nonhereditary cases. The detection of such a marker would be maximized by comparing unaffected carriers with nonhereditary cases. (36 refs)

78-6072 **The Relation of Gene Control Mechanis Cancer.** (Eng) Busch, H. (Dept. Pharmac Baylor Coll. Medicine, Houston, TX, 77030). *Z Krebs* 92(2): 123-135; 1978.

Recent experiments on the involvement of genetic r anisms in the cancer cell phenotype (growth and cell div invasiveness, and metastasis) are reviewed. Support fo idea that gene control of cancer cells is aberrant em from studies that suggest that aberrations in gene contro be rectifiable. Combined teratoma cells and normal tocyte cells produced normal heterozygous guinea pig normal controls produced in normal sequence in the bi cal clock were apparently capable of converting tera cells to normal cells. The direct controls of gene functio considered to be the nonhistone nuclear pro Studies showed that the nonhistone nuclear protei experimental hepatomas and nontumor tissues diff In other studies, different antigens were found i nuclear proteins of tumors and nontumor tissues. was nuclear antigen NAg-1, the first fetal chron proteins like NAg-1 or No-Ag-2, a nucleolar protein, be special stimuli that result in the transcription translation of messenger RNA species for the ca phenotype. There is uniform agreement that cancer exhibit characteristics that are uncontrolled by sys available to the host. However, it is possible that substa responsible for normal maturation at specific times of bryogenesis would function in tumor cells to reorder or e nate the specific readouts related to the cancer process. fetal readouts that may be responsible for the cancer ph type are likely to be timing errors of dislocated genom which proper timing may be restored by the substa normally involved in this reordering process. (24

78-6073 **Some Aspects of Human Tumor Genetics.** (I Pogosiants, E. E. (Oncological Res. Cen Moscow, USSR). *Vopr Onkol* 24(9): 15-24; 1978.

The role of genetic factors in cancer etiology is reviewed. most human tumors, genetic effects are of little importa but environmental factors are of paramount importa However, there are some rare tumors that are dependen specific inherited genes. In some cases, genetic markers responsible for the development of the tumor proper; in ers, they are responsible for the complex syndromes in wh a malignant tumor may be only one of the obligatory featu In other cases, a syndrome that predisposes to the deve ment of tumors and/or leukemia is inherited. The recent covery of the genetic heterogeneity of tumors at the same (including common tumors such as breast and renal can is of particular theoretical and clinical interest. (22 refs)

78-6074 **Mendelian Genetics and Cancer.** (Fre) An J. L. (Service de Medecine A, Institut G

ve-Roussy, 16 bis, avenue Paul-Vaillant-Couturier, F 94800 llejuif, France). *Bull Cancer (Paris)* 65(2): 131-136; 1978.

f approx 1,142 simple genetic patterns known to be associat- with 2,336 syndromes, about 200 are associated with high ncer risk. However, other factors such as the environment ay interact with these genes to affect cancer risk. It is some- nes difficult to distinguish between these factors. In nconi's anemia and xeroderma pigmentosum, there is predisposition to cancer development because of romosome instability. The role of the histocompati- lity system in evolution of certain cancers is discussed. ne most common hereditary syndromes associated with higher cancer risk are tabulated. (22 refs)

3-6075 **Malignant Neoplasms of Genetic Origin in *Drosophila melanogaster*.** (Eng) Gateff, E. (Bi- logisches Institut I-Zoologie, Albert-Ludwigs-Universitat, 3 Freiburg im Breisgau, W. Germany). *Science* 200(4349): 445-1451; 1978.

Malignant neoplasms that develop in recessive-lethal larval mutants of Drosophila melanogaster are described. There are x nonallelic mutants that develop malignant neuroblas- omas in the adult optic centers. These mutants, on chromo- omes 1, 2, and 3, represent developmental genes that prevent ifferentiation of the adult optic neuroblasts into adult optic eurons by causing an uncontrolled, autonomous, invasive, ethal, and transplantable growth of the adult optic neurob- asts and ganglion mother cells. Some neoplastic cells, even hough they are incapable of differentiation, retain parts of heir behavioral repertoire, whereas other neoplastic cells ecome unresponsive to hormonal signals. Eight reces- ive-lethal mutants develop imaginal disk neoplasms: five orm imaginal discs that grow in a compact, noninvasive fash- on, and three form neoplasms that grow in an invasive pat- ern. Morphological variations exist among imaginal isks from different mutant stocks, and neoplastic disks n situ as well as after transplantation possess qualities f both malignant and benign neoplasms. The presence f *y f* clones on the integument indicates nonautomomy nd a capacity of the homozygous tumor cell for reversal o the differentiating state; the absence of *y f* clones hows autonomy and an incapacity for reversal. A third ype of tumor mutation induces malignant neoplastic ransformation of the presumptive blood cells in the arval blood-forming organs (lymph glands). The mutant enes are located on chromosomes 1, 2, and 3. Plasmatocyte-type cells are the malignant component, nd they grow in an autonomous way; crystal cells do not participate in the growth after transplantation. The neoplastic state of the mutant blood cells in situ is not autonomous, but may result from a normal factor else- where in the animal. (54 refs)

78-6076 **Tumors Arising in Organ Transplant Recipi- ents.** (Eng) Penn, I. (Dept. Surgery, Univ. Colorado Sch. Medicine, Denver, CO). *Adv Cancer Res* 28: 31-61; 1978.

The development of cancer in organ transplant patients is reviewed. These patients can be classified into three groups: (1) those with inadvertently transplanted neoplasms; (2) those with cancer that arose de novo at some time after transplantation; and (3) those with tumors present before grafting. Data were collected on 65 patients who received organs (1 heart, the rest kidneys) from donors who had cancer. Six of the 13 organs from living donors contained neoplasms; one of these tumors spread locally and one caused distant metastases. Of the 52 cadaver organs, 20 contained cancer cells. Five remained localized to the kidney, 1 spread locally, and 14 caused distant metastases that were histologically identical to the original donor tumors. After transplantation, 5%-7% of patients develop tumors arising de novo. The incidence is 100 times greater than that in the general population of the same age range. Data are given for 548 recipients who developed 572 de novo tumors (24 patients had $>$ 1 type of cancer). These tumors were not related to the 12 preexisting recipient tumors treated from several weeks to 17 yr before transplantation or to any of the 6 tumors found among the 650 donors. Of 164 patients who had tumors removed at the time of or 5 yr prior to transplantation, 92 had no recurrence, 63 had a recurrence or metastases, 10 developed de novo cancers, and 1 case remained unchanged. Cancer in organ transplant recipients probably develops as a result of a complex interplay of multiple factors, including alterations in immunity, immunosuppressive agents or other drugs, genetic factors, and oncogenic viruses. (143 refs)

78-6077 **Tumor Immunity. An Overview.** (Eng) Siegel, B. V. (Dept. Pathology, Univ. Oregon Health Sciences Center, Portland, OR). *Am J Pathol* 93(2): 515-523; 1978.

From attempts to formulate specific modes of cancer therapy based on the ability of the immune system to recognize and destroy foreign antigens, it has become clear that tumorigenesis is affected by immunologic and nonimmunologic factors. Tumors may evade immunosurveillance by a number of mechanisms, including sneaking through, immunosuppression, antigenic modulation, serum blocking factor, antigen shielding, genetic resistance, and immunostimulation. An integral part of the immune response is the activation of macrophages, possibly through interferon, to a specifically cytotoxic state, which may be associated with the prevention of metastatic spread. Since much of the knowledge of immunologic mechanisms in tumor-cell killing has been gained from in vitro experiments, the relevancy of such observations to events in vivo remains unclear. However, tumor immunity may be enhanced by (1) amplification of cytotoxic T cell pathways; (2) modification of genetic restriction on immune response to tumor antigens; and (3) use of immunopotentiators to stimulate macrophage cytotoxicity and phagocytic activity. (37 refs)

78-6078 **Acute Lymphocytic Leukemia Involving Pre-B Cells.** (Eng) Vogler, L. B. (Cellular Immunobiology Unit Tumor Inst., Dept. Pediatrics & Microbiology, Univ. Alabama, Birmingham, AL); Crist, W. M.; Cooper, M. D.; Lawton, A. R. *In: Human Lymphocyte Differentiation: Its Application to Cancer. Proceedings of the International Symposium on Human Lymphocyte Differentiation: Its Application to Cancer, held in Montpellier (France) by Institut National de la Sante et de la Recherche Medicale and Delegation Generale a la Recherche Scientifique et Technique, 2-4 March, 1978.* Serrou, B., Rosenfeld, C., eds. (Amsterdam: North Holland Publishing Company): 423 pp.; 407-413; 1978.

Some of the characteristics of precursor B cells (pre-B cells) are described, and their participation in the proportion of childhood acute lymphoblastic leukemias is discussed. Pre-B cells contain cytoplasmic IgM (cIgM+) but they appear to lack functional antigen receptors and detectable surface IgM (sIgM). Large pre-B cells in humans divide rapidly, giving rise to smaller pre-B cells that are the direct precursors of sIg+ B lymphocytes; they resemble the sIg- lymphocytes that are the precursors of B lymphocytes in mice. Generation of antibody diversity appears to begin at the pre-B cell stage of differentiation. Lymphoblasts from 4/22 children with acute lymphocytic leukemia had the pre-B phenotype. Cells from all four patients bore the D locus related p23,30 antigen; a proportion of cIgM+ lymphoblasts from patients 2 and 4 expressed barely detectable sIgM, and Fc receptors were present on virtually all cells from patients 1 and 2. In patient 2, cIgM+ blasts from a lymph node were devoid of sIgM, whereas 75% of cIgM+ blasts from bone marrow stained immunoglobulins were not found in any patient. Chemotherapy resulted in remissions associated with the disappearance of cIgM+sIg- lymphoblasts from the blood in all four patients. (27 refs)

78-6079 **Macrophage Turnover and Traffic: A Review.** (Eng) Spector, W. G. (Dept. Pathology, St. Bartholomew's Hosp. Medical Coll., London, England). *In: The Macrophage and Cancer. Proceedings of the European Reticuloendothelial Society Symposium held in Edinburgh, September 12-14, 1977.* European Reticuloendothelial Society (Edinburgh, Scotland): 448 pp.; 15-18; 1977.

Current knowledge of the turnover rate of macrophages (MP) in different body states is reviewed. In steady-state conditions, the MP pool in sites such as the liver and peritoneum is maintained by a slow turnover of fresh MP from circulation and also by a process of mitotic division in situ. In inflammatory states, monocytes migrate to the site at a constant rate through interendothelial gaps in venules, and, once inside a lesion, they are converted to MP with enhanced phagocytic activity. Both processes probably depend on serum and humoral factors. Factors that accelerate monocyte release from marrow or initiate peritoneal MP mitosis in cell cultures have been discovered. Although there is a close correlation between hypersensitivity and chronic inflammation, it i known whether MP mobilization is linked to T-lymph activity. Complement, however, may be involved. MP occurs primarily by three mechanisms: endocytosis of material, mitosis with lethal chromosome aberrations, c mation of multinucleate giant cells. Both resident steady populations and inflammatory MP are probably involv carcinogenesis. (13 refs)

78-6080 **Mononuclear Phagocytes and Antitumor sistance: A Discussion.** (Eng) Keller, R. munobiology Res. Group, Univ. Zurich, Schonleinstrass CH-8032 Zurich, Switzerland). *In: The Macrophage Cancer. Proceedings of the European Reticuloendotheli ciety Symposium held in Edinburgh, September 12-14,* European Reticuloendothelial Society (Edinburgh, land): 448 pp.; 31-49; 1977.

The contribution of macrophages (MP) and MP-like ce host tumor resistance is reviewed. The numerous eff mechanisms by which MP alter the growth of other ce vivo and in vitro ordinarily depend on MP activation by cific or nonspecific means. This activation, expressed cytotoxic function, usually requires a latent period of 1 hr. An activated MP is capable of killing a variety of ta (in vitro). This effect transcends intra- and interspecific tocompatibility barriers, and it is independent of the t cell type or growth characteristics. However, MP-medi cytolysis shows some selectivity for transformed cells. mechanism of MP-mediated cytolysis is not understood, the process is resistant to x-rays and several metabolic in tors, requires energy, and possibly involves complement vation and proteases. In vivo studies have shown that passive transfer of activated MP can inhibit tumor gro and research is underway regarding the in vivo modifica of MP functions in the tumor-bearing host. Not only MP also nonphagocytic peritoneal cells, phagocytic lymphoid cells, cytotoxic lymphoreticular cells, and natural killer have been implicated in antitumor resistance. (106 refs)

78-6081 **The Influence of Tumour Cell Products on M rophage Function In Vitro and In Vivo.** (E James, K. (Dept. Surgery, Univ. Edinburgh Medical S Teviot Place, Edinburgh EH8 9AG, Scotland). *In: The M rophage and Cancer. Proceedings of the European Reticul dothelial Society Symposium held in Edinburgh, Septem 12-14, 1977.* European Reticuloendothelial Society (E burgh, Scotland): 448 pp.; 225-246; 1977.

The effects of viable tumors, tumor culture supernatants, tumor culture extracts on macrophage development function are reviewed. Animal studies in vivo and in v have shown that accumulation of macrophages and th chemotactic responses can be impaired by tumors or th soluble products. Some findings indicate that tumors m

air immunosurveillance against them or other tumors. nversely, macrophage number, activity, or chemotaxis y be enhanced by tumors. In vitro studies have usually cluded that chemotactic response of human blood mono- es is depressed by tumors. However, the factors influenc- macrophage function could also be of host cell or viral gin. The possible modes of tumor-macrophage interaction manifold: tumor products could interfere with the pro- tion of factors that modulate macrophage function, pre- t the necessary interaction of such factors, or tumor pro- ts themselves could have direct effects on macrophages. rmal macrophages may be sequestered at the tumor site , therefore, rendered inactive, or tumor products may in- it macrophage activity within a tumor. In any event, mac- hage development and motility can be adversely affected tumor cells placing the host at a distinct disadvantage. (61)

6082 **Anti-tumour Effects of Macrophages Injected into Animals: A Review.** (Eng) Den Otter, W. pt. Pathology, State Univ., Pasteurstraat 2, Utrecht, Ne- rlands); Dullens, H. F.; Van Loveren, H.; Pels, E. *In: The crophage and Cancer. Proceedings of the European ticuloendothelial Society Symposium held in Edinburgh, tember 12-14, 1977.* European Reticuloendothelial Socie- (Edinburgh, Scotland): 448 pp.; 119-141; 1977.

ta concerning cytotoxic macrophages, the local antitumor ct of macrophages injected into animals along with tumor ls, and the antitumor effect of macrophages injected at a distant from that of the tumor cells are reviewed. (67 refs)

6083 **Cancer of the Large Bowel with Special Reference to Incidence and Etiology.** (Eng) Baugh- n, B. B. (401 W. Main St., Frankfort, KY, 40601). *Am rg* 44(9): 548-553; 1978.

xt to lung cancer, large bowel cancer (LBC) is the ond most common cancer in the US, and it is much re common in people in the higher socioeconomic ata. This finding seems to be related to the fact that rsons with diets high in fats and proteins also show an reased incidence of LBC. Three premalignant con- ions are associated with LBC: adenomatous polyps, erative colitis, and congenital multiple polyposis. operative levels of carcinoembryonic antigen have n shown to correlate with the extent of the disease l prognosis for recurrence. (34 refs)

6084 **Etiology and Pathogenesis of Tumors.** (Rus) Diad'kova, A. M. (N. N. Petrov Oncological Res. Inst., USSR Ministry Public Health, Leningrad, USSR). *Vopr Onkol* 24(9): 3-7; 1978.

Recent studies on the etiology and pathogenesis of tumors are reviewed with special regard to viral carcinogenesis. Penetration of the carcinogenic agent (virus, chemical substance, or radiation) into the body, primary reactions of the body to the agent, cellular changes, and the appearance or existence of conditions necessary for or facilitating tumor development are the basic steps of carcinogenesis. These steps can be interrelated and simultaneous, but none of them alone determines the fate of the cellular changes Herpes virus type 2 and Epstein-Barr virus are suspected etiological agents in cervical carcinoma and Burkitt's lymphoma, respectively, in humans. (no refs)

78-6085 **Pathogenesis of Malignant Neoplasms Induced in Hamsters by the Oncogenic DNA Simian Virus 40 (SV40).** (Eng) Diamandopoulos, G. T. (Dept. Pathology, Harvard Medical Sch., Boston, MA, 02115). *Fed Proc* 37(7): 2082-2084; 1978.

Factors responsible for the morphogenesis of neoplasms induced in hamsters by simian virus 40 (SV40) were determined by inoculating random-bred Syrian golden hamsters with SV40 iv [$10^{8.5}$ median tissue culture infective dose ($TCID_{50}$)]. Six to 12 mo later, approx 90% of the hamsters developed lymphocytic leukemia, lymphoblastic lymphosarcoma, reticulum cell sarcoma, osteogenic sarcoma, and/or anaplastic sarcoma. Controls were tumor-free. Tumor antigen, tumor-specific transplantation antigen, and antibody to tumor antigen were found in the tumor-bearers. Similar results were were obtained with three inbred hamster lines. Reticulum cell sarcoma cells lost their original morphology soon after dissociation into suspensions, but preserved their phagocytic activity throughout many in vitro passages. Osteogenic sarcoma cells lost both their differentiated phenotype and their capacity to form osteoid during serial passage. Both the lymphocytic and the lymphoblastic neoplastic cells preserved their lymphoid morphology and their ability to produce immunoglobulin after an indefinite number of in vitro passages. The effect of hamster age and virus dose on SV40-induced tumor development was studied. Random-bred 3-wk- to 12-mo-old hamsters received $10^{8.5}$ $TCID_{50}$ of SV40 iv, and groups of 3-wk-old hamsters were inoculated iv with SV40 aliquots of progressively decreasing titers. Tumor incidence and, to a lesser extent, tumor latency were directly dependent on the age of the animals at the time of virus exposure and on virus dose. The results suggested that cell replication at the time of oncogenic exposure enhances its susceptibility to transformation. Three strains of 3-wk-old inbred hamsters received $10^{7.5}$ $TCID_{50}$ iv, and tumor incidence and latency were approx the same in all three; however, random-bred hamsters were almost completely resistant under identical conditions. These results could be due to genetic differences, control at the cell-response level, or differences in immunological capacity. (15 refs)

78-6086 **Virus Oncogenes and Carcinogenesis.** (Rus) Zhdanov, V. M. (D. I. Ivanovskii Inst. Virology, Acad. Medical Sciences USSR, Moscow, USSR); Al'tshtein, A. D. *Vopr Onkol* 24(9): 8-15; 1978.

Recent studies of viral oncogenes are reviewed with special regard to those of polyoma viruses, adenoviruses, and oncornaviruses. Each nondefective oncornavirus has three genes that are necessary for its reproduction: (1) *env*, coding for the precursor of the principal glycoprotein and low-mol-wt membrane proteins; (2) *pol*, coding for the synthesis of reverse transcriptase; and (3) *gag*, coding for the precursor of the internal structural proteins of the virion. Defective viruses are replicated by complementation with a helper virus. The simian virus 40 genome has only three genes: *A*, which codes for the nonstructural proteins synthesized before replication of virus DNA; *BC*, which codes for the synthesis of the main structural protein VP-1; and *D*, which codes for the synthesis of structural proteins VP-2 and VP-3. Most adenoviruses, including those that are not oncogenic in vivo, are able to transform cells in vitro. Virus-specific T and S antigens are always present in the adenovirus-transformed cells. These antigens appear to be coded by the adenovirus oncogene, and they are responsible for the cell transformation. The characteristics of the viral oncogenes suggest that they are cellular in origin. As a result of these studies, it is suggested that nonviral oncogenesis is due to a disturbance in the functioning of certain cellular genes, as a result of which they are transformed into endogenous oncogenes. (53 refs)

78-6087 **The Gene Order of Avian RNA Tumor Viruses Derived from Biochemical Analyses of Deletion Mutants and Viral Recombinants.** (Eng) Wang, L. H. (Rockefeller Univ., New York, NY, 10021). *Annu Rev Microbiol* 32: 561-592; 1978.

The various experimental approaches that led to determination of the gene order of avian RNA tumor viruses are reviewed. Through biochemical analyses of deletion mutants and viral recombinants, the gene order 5′-gag-pol-env-src-c-3′ can be drawn for sarcoma viruses and 5′-gag-pol-env-c-3′ for leukosis and transformation-defective viruses. (180 refs)

78-6088 **Bovine Leukemia Virus Involvement in Enzootic Bovine Leukosis.** (Eng) Burny, A. (Dept. Molecular Biology, Univ. Brussels, 1640-Rhode St-Genese, Brussels, Belgium); Bex, F.; Chantrenne, H.; Cleuter, Y.; Dekegel, D.; Ghysdael, J.; Kettmann, R.; Leclercq, M.; Leunen, J.; Mammerickx, M.; Portetelle, D. *Adv Cancer Res* 28: 251-311; 1978.

The major achievements of research over the last 20 yr on the role of bovine leukemia virus (BLV) in enzootic bo leukosis are reviewed. According to its high-mo RNA-reverse transcriptase complex, structural proteins their mode of maturation, and general morphology, BL considered a retrovirus belonging the subgroup C mamm an oncornaviruses. However, this virus is unique in its w of budding, the strict Mg^{2+} requirement of its reverse t scriptase, and its property of inducing syncytia in monol cultures of nontransformed cells. In addition, neither mol lar hybridization nor antigenic cross-reactivity occurs any of the known RNA oncogenic viruses. BLV is an ex nous infectious agent. Persistent lymphocytosis (PL) is a clinical form of enzootic bovine leukosis--a percentage of lymphocytes are tumor cells containing BLV proviral D sequences. Infected animals actively synthesize antibodie BLV, and there are several serologic methods of detec BLV antibodies. BLV produced in culture can infect ca sheep, goats, and chimpanzees, and it has induced tumor PL in calves, sheep, and goats. Only a fraction of infe animals develop tumors. Virus dose, age at infection, genetic make-up of the recipient appear important in de mining the final outcome of the interaction between host virus. (334 refs)

78-6089 **Epstein-Barr Virus: The Ravager.** (Eng) Go stein, J. C. (Div. Otolaryngology, Albany Me cal Center, Albany, NY, 12208); Parulekar, S. S.; Paones D. F.; Rapoport, A.; Kouyoumgian, J. *Ann Otol Rhi Laryngol* 87(5, part 1): 729-735; 1978.

The role of Epstein-Barr virus in infectious mononucleo Burkitt's lymphoma, and nasopharyngeal carcinoma is viewed. (26 refs)

78-6090 **Malignant Tumors Induced by Human Pa loma Virus.** (Pol) Jablonska, S. (Klinika D matologiczna AM, ul. Koszykowa 82a, 02-008 Warsaw, land); Orth, G.; Jarzabek-Chorzelska, M.; Rzesa, G.; Obal S.; Glinski, W.; Favre, M.; Croissant, O. *Przegl Derma* 65(5): 497-507; 1978.

Studies of human papilloma viruses (HPV) are reviewe HPV 3 induces both flat warts and a form of epidermod plasia verruciformis (EV) characterized by lesions similar flat warts. HPV 3 has slight, if any, oncogenic potential, HPV 4, which also induces EV, is oncogenic. EV due to H 4 is characterized by very flat, reddish wartlike lesions, plaques flush with the skin, hyperpigmentation reminisc of pityriasis versicolor, and depigmentation. HPV 1, whi induces plantar warts, and HPV 2, which induces comm warts, do not seem to be oncogenic. Depressed cell-mediat immunity is of great significance in the dissemination a

istence of warts, especially flat warts, and EV. However, gnant transformation is due mainly to HPV 4. The possi- y that specific vaccines can prevent transformation in pa- ts with HPV-4 induced EV is discussed. (60 refs)

6091 **The Human Papillomaviruses.** (Eng) Orth, G. (Unite de Recherches sur l'etiologie virale des cers humains, Laboratoire no. 147 associe au CNRS, te 140 de l'INSERM, Institut Gustave-Roussy, 16 bis, nue P. Vaillant-Couturier, F 94800 Villejuif, France); Ja- nska, S.; Breitburd, F.; Favre, M.; Croissant, O. *Bull Can- (Paris)* 65(2): 151-164; 1978.

a on the properties and pathogenicity of human papil- aviruses (HPV's), the lesions induced by HPV's, in vivo s-cell interactions, and factors involved in the production arcinomas by papillomaviruses are reviewed. Recent bio- mical and serological studies have shown the existence of east four distinct types of HPV's that cause benign skin ons. These viruses show hardly any antigenic relation- s; their DNA's differ by their sensitivity to restriction onucleases and show little, if any, sequence homology in lecular hybridization experiments using complementary A's transcribed in vitro. Data on the pathogenicity of Vs are incomplete, but they indicate that some types of ign skin lesions (plantar warts, common warts, flat warts) y be preferentially associated with certain types of HPV. dermodysplasia verruciformis (EV) is associated with two es of HPV, HPV-3 and HPV-4. The lesions produced by se two viruses differ. Of a series of 13 EV patients, malig- t transformation occurred in only 1/8 with HPV-3, which duces flat, wart-type lesions and hyperpigmented plaques, intraepidermal or invasive carcinomas were observed in 5 patients infected with HPV-4, which produces reddish l pityriasis versicolor-like plaques. This suggests that at st one HPV may have oncogenic potential, as do rabbit ope) papillomavirus and bovine alimentary tract papil- navirus. (82 refs)

-6092 **Polyoma Virus, as a Model for Viral Skin Carcinogenesis.** (Eng) Meyer, G. (Unite 119 de NSERM, 27 boulevard Lei-Roure, F 13009 Marseille, ance). *Bull Cancer (Paris)* 65(2): 145-150; 1978.

lyoma (Py) virus, the simplest model of transformation by DNA virus, is characterized along with Py virus-sensitive ls, virus/cell interactions, perpetuation of viral informa- n, and the mechanism of Py virus-induced malignant nsformation. Py virus is a small (45-mμ) DNA virus with ic symmetry and without an envelope. Its capsid is com- sed of 72 capsomers forming an icosahedral structure. The us contains a nucleic acid having a mol wt of 3.6×10^6 daltons, and the DNA is supercoiled. Three types of cells are sensitive to Py virus: cells that allow a complete virus cycle to take place, cells that do not allow maturation of infectious virions, and cells with intermediate properties. Three possible virus/cell interactions are reviewed: lytic infection, abortive infection, and malignant transformation. Perpetuation of viral information begins after penetration of viral DNA into the nucleus, with the production of early proteins (tumor and surface antigens), the induction of cellular DNA synthesis followed by viral DNA synthesis, the production of late proteins (virus antigen), and cell lysis. Nuclear and surface antigenic modifications are correlated with the mechanism of transformation in vitro and in vivo. (9 refs)

78-6093 **Structural Organization of Papovavirus and Adenovirus DNA.** (Rus) Roninson, I. B. (D. I. Ivanovskii Inst. Virology, Acad. Medical Sciences USSR, Moscow, USSR); Naroditskii, B. S. *Vopr Med Khim* 24(5): 579-591; 1978.

Studies of the structural organization and specific fragmentation of DNA in papova- and adenoviruses are reviewed with special regard to simian virus 40 and adenovirus 2. (142 refs.)

78-6094 **Structure and Morphogenesis of Type-C Retroviruses.** (Eng) Montelaro, R. C. (Dept. Surgery, Duke Univ. Medical Center, Durham, NC, 27710); Bolognesi, D. P. *Adv Cancer Res* 28: 63-89; 1978.

Models for the structure and morphogenesis of avian and murine C-type retroviruses were derived from an extensive review of literature concerning retrovirus morphogenesis. The models are based on the molecular arrangement of virion structural components in the particle as well as on available data relating to the biosynthesis of these products. (128 refs)

78-6095 **Herpes Simplex Virus Type 2 and Cervical Cancer.** (Dut) te Velde, E. R. (Afdelingen Gynaecologie, Academisch Ziekenhuis, Utrecht, Netherlands); The, T. H. *Ned Tijdschr Geneeskd* 122(33): 1226-1230; 1978.

Epidemiological and virological studies show a correlation between herpes simplex virus 2 (HSV-2) infection and carcinoma of the uterine cervix, which suggests that HSV-2 may be involved in the etiology of this carcinoma. (12 refs)

78-6096 **Chemical-Viral Interactions in Carcinogenesis.** (Eng) Weinstein, I. B. (Inst. Cancer Research, Columbia Univ. Coll. Physicians and Surgeons, New York, NY). *In: Prevention and Detection of Cancer. Proceedings of the Third International Symposium on Detection and Prevention of Cancer Held by the International Study Group for the Detection and Prevention of Cancer in New York, April 26 - May 1, 1976.* International Study Group for the Detection and Prevention of Cancer. (New York, NY): Vol. 2(part 1), 2404 pp.; 1609-1620; 1978.

Studies on the possible role of RNA viruses in the transformation of epithelial cells by chemical carcinogens are reviewed. In 1972, it was discovered that cell cultures established from rat hepatomas induced by aromatic amine carcinogens synthesize RNA viruslike particles. Electron micrographs revealed that these included intracisternal A particles, enveloped A particles, and, more rarely, mature C particles. Almost all rodent cell cultures established from tumors induced by aromatic amine carcinogens, polycyclic aromatic hydrocarbons, or asbestos synthesized RNA viruslike particles, as did rat epithelial cell cultures transformed in vitro. All attempts to detect RNA viruses in human cancers were negative. Further studies indicated that viruslike particles associated with chemically induced rodent tumors lacked biologic activity. This result is consistent with studies indicating that although RNA viruslike particles or their biochemical markers can be demonstrated frequently in spontaneous and radiation- or chemically-induced rodent tumors, these particles only rarely induce neoplasia when introduced into normal animals. There is no direct evidence that virus activation plays a causal role in the induction of carcinoma in animals or humans by radiation or chemical carcinogens. The viruslike particles and virus-related sequences in spontaneous and chemical carcinogen-induced neoplasms may play the role of a cofactor in carcinogenesis. (30 refs)

78-6097 **Recombinant Origins of Leukemogenic Murine Viruses (Parke-Davis Award Lecture, 1978).** (Eng) Lerner, R. A. (Dept. Cellular and Developmental Immunology, Res. Inst. Scripps Clinic, 10666 N. Torrey Pines Rd., La Jolla, CA, 92037). *Am J Pathol* 93(1): 9-26; 1978.

Four points concerning retroviral genes and their hosts are derived using data on murine systems, although much of the information can be generalized to other species, including primates. (1) Retroviral genes, as proviruses, comprise an extensive multigene family. (2) As with host genes, proviral expression is regulated during development and differentiation. (3) Members of the retroviral gene family are constructed out of functionally distinct modules. (4) Viruses with new or altered pathogenicity may be constructed from nonpathogenic members of the multigene family. The last point is the most important. Within the infinite reassortment and rangement processes that occur by recombination, biolog ly distinct viruses with unique pathogenicity can be structed. The generation of virion diversity is said to o by a somatic recombination of proviruses. What makes concept more interesting is that the provirus encodes no differentiation molecules of the mouse. Thus, recombina not only generates virus but also alters differentiation m cules within the adult lifetime of the mouse. Neoplastic version is envisioned to take place within this framework a somatic mechanism is responsible for changing the cell face in mice. (20 refs)

78-6098 **Recent Studies on the Role of the Immune sponse in Resistance to Virus-induced kemias and Lymphomas.** (Eng) Meruelo, D. (Dept. Path gy, New York Univ. Medical Center, 550 First Ave., York, NY, 10016); McDevitt, H. O. *Semin Hematol* 1 399-419; 1978.

The contributions of immunogenetics to the understan of the influence of immune surveillance on neoplasia, part larly leukemias and lymphomas, are reviewed. The m murine histocompatibility complex, *H-2*, plays a large in the susceptibility and resistance of mice to virus-indu leukemia. The *H-2k/k* haplotype results in >90% incid of leukemia in one crossed strain. *H-2*-linked immune sponse genes (involved in the immune response to virus tumor-specific transplantation antigens) seem to be dire involved in conferring resistance to the development of ma nancy. The *H-2* complex plays a major role in determi the specificity of T cells sensitized against a variety of a gens, including viruses, tumor-associated antigens, antig induced by chemical modification of the cell surface, aut tigens, and non-*H-2* histocompatibility antigens. Two mo have been proposed to explain the requirement for *H-2* c patibility in these cytotoxic T-cell responses. A product of *H-2K* or *H-2D* region may interact with a virus or hap on a cell membrane, resulting in a new antigen recogni by effector T cells, or the interaction of T cells with ta cells, may involve a dual recognition system, with one re ing an *H-2* gene product. A second immune response g locus, separate from *Rgv-1*, may be responsible for confer resistance specifically to Friend and radiation leuke virus-induced neoplasia. Following intrathymic Rad inoculation, there is an increase in the cell-surface expres of *H-2K* and *H-2D* molecules on thymocytes of both susce ble and resistant mice, but *H-2D* molecules are increased a longer period of time in resistant mice. Immunogenetic s dies have begun to make an impact on human disease, evidenced by the finding that children with acute lymp blastic leukemia (ALL) expressing the *HL-A9* antigen h increased survival over other ALL patients. (127 refs)

-6099 **The Need for a Mammalian Test System for Chemical Mutagens and Carcinogens (Meeting stract).** (Eng) Stich, H. F. (Environmental Carcinogenesis nit, British Columbia Cancer Res. Centre, Vancouver, B. , Canada); Wei, L.; Whiting, R. *Can J Genet Cytol* 20(3): 7; 1978. (no refs)

-6100 **International Programme for the Evaluation of Short-Term Tests for Carcinogenicity.** (Eng) hby, J. (Central Toxicology Lab., Imperial Chemical Industries Ltd., Alderley Park, Nr. Macclesfield, Cheshire K10 4TJ, England); de Serres, F. J. *Mutat Res* 54(2): 3-206; 1978.

n international collaborative study was initiated to evaluate 5 mutagenicity assay systems (prokaryotic, eukaryotic, and ongenetic) for their ability to predict chemical carnogenicity, using 42 reference carcinogens and noncarcinoens. The response of each assay will be compared with carnogenicity findings for each chemical, and divergences etween individual assay results and carcinogenicity data will e viewed within the context of the response of other assays. o refs)

3-6101 **Organic Trace Analysis Using Direct Probe Sample Introduction and High Resolution Mass pectrometry.** (Eng) Haddon, W. F. (Western Regional Res. enter, US Dept. Agriculture, Albany, CA, 94710). *In: Symosium on High Performance Mass Spectrometry: Chemical pplications held in Lincoln, November 3-5, 1976.* University f Nebraska, National Science Foundation, AEI Scientific, nd INCOS Corp. 358 pp.; 97-119; 1978.

igh-resolution selected ion monitoring measurements on mples introduced on a direct probe can provide accurate nd highly specific qualitative and quantitative information out compounds present in trace amounts, even compounds f low volatility or chemical instability. Highest sensitivities re obtained for substances with large mass defects, such as alogenated pesticides and mycotoxins. (40 refs)

8-6102 **Analytical and Biological Analyses of Test Materials from the Synthetic Fuel Technologies. II. Extended Genetic and Biochemical Studies with Mutagenic Fractions.** (Eng) Rao, T. K. (Biology Div., Oak idge Natl. Lab., Oak Ridge, TN, 37830); Young, J. A.; Hardigree, A. A.; Winton, W.; Epler, J. L. *Mutat Res* 54(2): 185-191; 1978.

Certain highly mutagenic fractions of the crude synthetic fuel Synfuel A-3 were subjected to extensive genetic and biochemical analyses. Slight (not more than two-fold) mutagenic activity was noted with all fractions when the *Salmonella typhimurium* strain that detects base-pair substitution (TA1535) was used; metabolic activation was required. Strains that detect frameshift mutations (TA1537, TA1538, and TA98) were more sensitive to the fractionated Synfuel. TA1538 and TA98 exhibited a 20- to 75-fold increase over the spontaneous mutation rate when metabolic activation with various induced rat liver microsomal fractions (S-9) was included. Qualitative differences were seen with different induced S-9 preparations, and rat liver enzymes were the rate-limiting factor in the activation of the highly active basic fraction. The data indicate that the mutagenicity of Synfuel A-3 occurs by a frameshift mechanism and that the fuel contains chemical mutagens requiring metabolic transformation for conversion into an active form. (12 refs)

78-6103 **High-Pressure Liquid Chromatographic Analysis of Arylhydroxylamines after Derivatization with Methyl Isocyanate.** (Eng) Sternson, L. A. (Dept. Pharmaceutical Chemistry, McCollum Labs., Univ. Kansas, Lawrence, KS, 66044); DeWitte, W. J.; Stevens, J. G. *J Chromatogr* 153(2): 481-488; 1978.

A method for the analysis of micromolar levels of arylhydroxylamines in liver homogenates is described. The arylhydroxylamine is extracted with dichloromethane and then converted to the corresponding N-hydroxyurea by reaction with methyl isocynate prior to high-pressure liquid chromatographic separation. This procedure renders the reaction product stable in soln, and it converts the hydroxylamine to a species that can be distinguished from other amine metabolites and metabonates. (18 refs)

78-6104 **Further Evaluation of a Hamster Embryo Cell Carcinogenesis Bioassay.** (Eng) Pienta, R. J. (NCI Frederick Cancer Res. Center, Frederick, MD, 21501); Poiley, J. A.; Lebherz, W. B. *In: Prevention and Detection of Cancer. Proceedings of the Third International Symposium on Detection and Prevention of Cancer Held by the International Study Group for the Detection and Prevention of Cancer in New York, April 26 - May 1, 1976.* International Study Group

for the Detection and Prevention of Cancer. (New York, NY): Vol. 2(Part 1), 2404 pp.; 1993-2011; 1978.

A standardized Syrian hamster embryo cell carcinogenesis bioassay was established, and results of its evaluation with 77 known carcinogens showed a high correlation (89%) with the reported carcinogenicities of these chemicals. No false-positive results were obtained with noncarcinogens, and spontaneous transformation was never observed in untreated cultures. However, until further evaluations are made, chemicals with negative responses cannot necessarily be considered noncarcinogenic. (11 refs)

78-6105 **Mutagenicity of Ozonated, Recycled Water.** (Eng) Gruener, N. (Gulf South Res. Inst., New Orleans, LA, 70186). *Bull Environ Contam Toxicol* 20(4): 522-526; 1978.

The mutagenicity of ozonated and nonozonated recycled water was tested in the Salmonella/microsome system. Recycled water was concentrated by low-pressure, low-temperature (37-38 C) distillation, and the recovery of organics [measured as total organic carbon (TOC)] in the concentrates was 95%. The mutagenicity of this concentrated water, containing 20-250 μg TOC/plate, was tested in *Salmonella typhimurium* strains TA100 and TA98 with and without microsomes. Results were negative at these levels; higher levels of TOC could not be tested because of toxicity. Water ozonated for 15 min contained 25% less organics and was mutagenic to both TA100 and TA98. Microsomal activation was not required in either strain but with strain TA98, the presence of rat liver microsomes resulted in an additional increase in the number of mutants. The specific mutants formed during ozonation were not identified. (8 refs)

78-6106 **Rat Liver Microsome-mediated N-Demethylation and Mutagenicity of Azoxymethane.** (Eng) Campbell, R. L. (Procter and Gamble Co., Miami Valley Labs., P.O. Box 39175, Cincinnati, OH, 45247); Suppnick, J. D.; Hettrick, J. M.; Nigro, N. D. *Cancer Res* 38(12): 4585-4590; 1978.

The rat liver microsome-mediated metabolism of azoxymethane (AOM) to formaldehyde was studied in vitro. A mutagen reverting *Salmonella typhimurium* strains HisG46, TA1530, TA1535, and TA100 was detected in incubations of AOM (13.6 mM) with liver microsomes and NADPH. Mutagen production was dependent on the length of incubation and on microsomal protein and AOM concentration. Detection of the mutagen was most sensitive with strain TA100. The N-demethylation (N-DM) of AOM to formaldehyde by liver microsomes required NADPH and O_2, thus exhibiting mixed-function oxidase characteristics. Phenobarbital (80 mg/kg/day, 3 days) or 3-methylcholanthrene (40 mg/kg/day, 2 days) pretreatment of the rats did not significantly alter the specific activity of microsomal AOM N-D but it did increase microsomal cytochrome P-450 levels 164% and 40%, respectively. Cobaltous chloride (60 mg/ sc) reduced AOM N-DM by 49% and cytochrome P-450 69%. SKF-525A in vitro inhibited AOM N-DM (43% init activity at 3 mM), but 7,8-benzoflavone did not. Disulfir reduced microsomal AOM N-DM by 70% when given 0.25% (wt/wt) in the diet, but it did not alter cytochro P-450 levels. The specific activity of microsomal AO N-DM was 86% greater when animals were fed a rat ch diet than when they were fed a semisynthetic diet containi 56% dextrose, 25% casein, 7% salt mix, 5% corn oil, 5 bran, and 2% vitamin supplement. Compared with a ser synthetic diet control, AOM N-DM was increased 55% a 175%, respectively, in animals fed a semisynthetic diet o rat chow diet and then starved 18 hr. The addition of 30 beef fat, however, did not alter the level of AOM N-D Since beef fat enhances AOM intestinal carcinogenesis, t mechanism by which dietary fat enhances tumorigenesis m not be related to metabolism of the carcinogen but rather promotional factors. (28 refs)

78-6107 **Inhibition of the Metabolism of the Colon Ca cinogen, Azoxymethane, by Pyrazole.** (En Fiala, E. S. (Naylor Dana Inst., American Health Found tion, Valhalla, NY, 10595); Kulakis, C.; Christiansen, C Weisburger, J. H. *Cancer Res* 38(12): 4515-4521; 1978.

To provide further evidence for the function of alcohol deh drogenase in the metabolism of methylazoxymethan (MAM) and its precursor, azoxymethane (AOM), the effec of pyrazole (PZ), an inhibitor of this enzyme, on AOM m tabolism were studied in vivo and in vitro. Male F344 ra treated with ^{14}C-AOM (10.5 mg/kg, sc) alone (controls) e haled approx 36% of the dose in 6 hr as $^{14}CO_2$, whereas ra pretreated with PZ (40 mg/kg, ip) exhaled approx 3.5%. Pr treatment of rats with 360 mg/kg PZ inhibited exhalation $^{14}CO_2$ for at least 6 hr. After 48 hr, the amount exhaled $^{14}CO_2$ comprised approx 50% of the do in controls and 26% and 20% in the 40- and 360-mg/k PZ-pretreated rats, respectively. Pretreatment wi 40 mg/kg PZ increased urinary MAM levels 2.5-fo compared with controls; pretreatment with 360 mg/k increased the urinary AOM levels 2.5- to 3-fold. I contrast to controls and 40-mg/kg PZ-pretreated rat 360-mg/kg PZ-pretreated animals showed increased u nary excretion of ^{14}C-methylamine and continued ^{14}C-MA excretion during the 24- to 48-hr period after labeled AO administration. Washed liver microsomes from PZ-treate rats converted AOM to MAM at the same rate as control but the hydroxylation was inhibited by adding PZ to the incu bation medium. These results show that PZ inhibits the me tabolism of AOM by at least two steps. At 40 mg/kg, PZ inhibits MAM oxidation, presumably by blocking alcoho dehydrogenase. At 360 mg/kg, it blocks this reaction an inhibits the hydroxylation of AOM. (27 refs)

108 **Failure of Ethyl Alcohol to Induce Dominant Lethal Mutations in Wistar Rats or to Syner-the Effect of X-rays in Swiss Mice (Meeting Abstract).**) Chauhan, P. S. (Bio-Medical Group, Bhabha Atomic Centre, Trombay, Bombay 400085, India); Aravindak-, M.; Sundaram, K. *Mutat Res* 53(2): 165-166; 1978. (no

5109 **Deuterium Isotope Effect in Bioactivation and Hepatotoxicity of Chloroform.** (Eng) Pohl, R. (Lab. Chemical Pharmacology, Natl. Heart, Lung, Blood Inst., Bethesda, MD, 20014); Krishna, G. *Sci* 23(10): 1067-1072; 1978.

details of the formation of phosgene ($COCl_2$) from chlo-rm ($CHCl_3$), including the electron transfer pathway and rate-determining step, were monitored by the use of the erium isotope. When unlabeled $CHCl_3$ was incubated liver microsomes from male Sprague-Dawley rats given jections of phenobarbitol (80 mg/kg), $COCl_2$ was readily duced. This reaction was NADPH-dependent and was bited by carbon monoxide or SKF 525-A, which suggest-that cytochrome P-450 catalyzed formation of $COCl_2$. en deuterium-labeled chloroform ($CDCl_3$) was substitut-for $CHCl_3$, $COCl_2$ production was significantly curtailed; refore, the cleavage of the C-H bond was the rate-deter-ing step of the reaction. The hepatotoxicity of $CDCl_3$ and Cl_3 (2.49 and 4.98 nanomoles/kg ip) was determined by asuring SGPT levels and by histologic examination. CDCl as less hepatoxic than $CHCl_3$ producing only minor histo-ical changes (as opposed to highly elevated levels). These dings implicate the oxidative dechlorination mechanism in bioactivation and subsequent carcinogenicity of chloro-m. (29 refs)

6110 **Carcinogenic Effects of Chronic Exposure to Very Low Levels of Toxic Substances.** (Eng) o, R. (Dept. Regius Professor Medicine, Radcliffe Infir-ry, Oxford OX2 6HE, England). *Environ Health Perspect* 155-159; 1978.

e effects of chronic exposure to very low levels of carcino-is are examined from a statistical point of view. The results icate that at low dose rates, the age distribution of extra nors is independent of the dose rate and that the expected mber of extra tumors is simply proportional to the dose e. Because of statistical uncertainties in the differences be-een the numbers of tumors found in a control group and reated group of animals, cancer risks $< 10\%$ cannot be urately characterized. Because of this, much work has ie into the fitting of mathematical models. Although the ails of the results in any particular case will depend on the ails of the models they happen to fit, the qualitative con-sions reached would have been reached whatever class of models had been fitted. Therefore, these conclusions are valid as a basis for legislation. (3 refs)

78-6111 **Best-Estimate Low-Dose Extrapolation of Carcinogenicity Data.** (Eng) Guess, H. A. (Environmental Biometry Branch, Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC, 27709); Crump, K. S. *Environ Health Perspect* 22: 149-152; 1978.

A low-dose extrapolation technique was developed for dichotomous data and used to analyze carcinogenicity data for vinyl chloride, dieldrin, 1,1,1-trichloro-2,2-bis-(p-chlorophenyl)ethane (DDT), dimethylnitrosamine, and ionizing radiation. The results suggest that when the very flat and the gradually sloping (linear or nearly linear) dose-response curves are considered together, it is extremely difficult on mathematical grounds to reject the hypothesis that the dose-response curve is nearly linear in the dose range corresponding to increased risks over a background of $\leq 10^{-6}$. These results have implications both for test design and for risk assessment. They suggest that if the hypothesis of a nearly linear dose-response curve in the low-dose range cannot be ruled out by assumption, then it seems questionable that it can be rejected by the data, even in cases in which it may be false. (no refs)

78-6112 **Interactions of Vinyl Chloride with Rat-Liver DNA In Vivo.** (Eng) Green, T. (Imperial Chemical Industries Ltd., Central Toxicology Lab., Alderley Park, Cheshire SK10 4TJ, England); Hathway, D. E. *Chem Biol Interact* 22(2/3): 211-224; 1978.

The reaction of vinyl chloride (VC) with liver DNA in Wistar rats and the reaction of chloroacetaldehyde (CAA) and calf thymus DNA were investigated. 9β-D-2′-Deoxyribofuranosylimidazo(2,1-i)purine (ethenodeoxyadenosine) and 1β-D-2′-deoxyribofuranosyl-1,2-dihydro-2-oxoimidazo(1,2-c)pyrimidine (ethenodeoxycytidine) were identified in the enzyme hydrolysates obtained (1) from calf thymus DNA that had been modified by chemical reaction with CAA and (2) from liver DNA prepared from rats that had been exposed po to VC in their drinking water (250 ppm) for approx 2 yr. Thus, VC-derived chloroethylene oxide and/or CAA behaved as a bifunctional alkylating agent toward deoxyadenosine and deoxycytidine residues of DNA. It is concluded that modification of the DNA structure by VC, through imidazo-cyclization of deoxyadenosine and deoxycytidine residues and through depurination of the resulting ethenodeoxyadenosine residues, is related to the mutagenicity of VC. The carcinogenicity of VC in animals and in humans and its mutagenic properties after biotransformation (by microsomal enzymes) into the active metabolites chloroethylene oxide and CAA, which show electrophilic reactivity toward DNA, would appear to conform with the

idea of a relationship between carcinogenesis and mutagenesis. (41 refs)

78-6113 **The Mutagenicity and Metabolism of 1,2-Dichloroethane (Meeting Abstract).** (Eng) Rannug, U. (Environmental Toxicology Unit, Wallenberg Lab., Univ. Stockholm, Stockholm, Sweden); Ramel, C. *Mutat Res* 53(2): 251-252; 1978. (1 ref)

78-6114 **Report on Carcinogenesis Bioassay of 1,2-Dichloroethane (EDC).** (Eng) National Cancer Institute (U.S. Dept. Health, Education, and Welfare, NIH, NCI, Bethesda, MD, 20014). *Am Ind Hyg Assoc J* 39(11): A26-A30; 1978.

The halogenated solvent 1,2-dichloroethane (ethylene dichloride, or EDC) was administered to rats and mice for 78 weeks at time-weighted av dosages of 95 mg/kg/day (high dose) and 47 mg/kg/day (low dose) in a carcinogenesis bioassay. In male rats, EDC caused forestomach cancers, multiple hemangiosarcomas, and subcutaneous fibromas. In female rats, EDC induced mammary cancers, appearing in some high-dose animals as early as the 20th week. EDC also caused breast and uterine cancers in female mice and respiratory tract cancers in both male and female mice. (no refs)

78-6115 **Macromolecular Binding and Metabolism of the Carcinogen 1,2-Dibromoethane.** (Eng) Hill, D. L. (Kettering-Mayer Lab., Southern Res. Inst., 2000 Ninth Ave., S. Birmingham, AL, 35205); Shih, T. W.; Johnston, T. P.; Struck, R. F. *Cancer Res* 38(8): 2438-2442; 1978.

Biochemical mechanisms related to the activation and inactivation of the carcinogen 1,2-dibromoethane (1,2-DBE) were investigated. In rats inoculated ip with 1,2-^{14}C-1,2-DBE [30.4 μCi; 4.2 micromoles (μmol)]: 0.2 ml ethanol, measurable amounts of radioactivity became bound to protein, RNA, and DNA of all major tissues. For each macromolecules class, the largest amounts of bound radioactivity were in the liver and kidneys. Optimum conditions for the rat liver glutathione S-transferase that uses 1,2-DBE as a substrate were established. The pH optimum was 8.2, the Km for 1,2-DBE was 25 mM, and Vmax was 2.1 μmol/min/g liver. Considerable enzyme activity was found in rat kidney; detectable activity was present in lung, testis, spleen, and heart. Enzymatic activity leading to the irreversible binding of radioactivity from ^{14}C-1,2-DBE to proteins in the reaction system was present in rat liver microsomes. The activity was inducible by phenobarbital but not by benz[a]anthracene. NADPH was required for activity of both the noninduced and the induced reactions; $MgCl_2$ stimulated both reactions. Bromoacetaldehyde, a reactive compound probably involved in the irreversible binding, was identified as a metabolite formed in the reaction system. Radioactivity from ^{14}C-1,2-DBE also became bound to crosomal proteins by a nonenzymatic chemical reaction. enzymatic reaction leading to binding to macromolec and/or the chemical binding reaction may be involved in biological activity of 1,2-DBE. (22 refs)

78-6116 **Mutagenicity of Industrial Compounds Eval ed by Means of Yeast Genetic Systems (M ing Abstract).** (Eng) Fumero, S. (Istituto di Ricerche omediche 'A. Marxer', Ivrea, Italy); Mondino, A.; Barale, Loprieno, N. *Mutat Res* 53(2): 189; 1978. (no r

78-6117 **Preliminary Report on the Possible Use of N ronal Tissue Culture in Carcinogenesis In Vi** (Eng) Boulos, B. M. (Sch. Public Health, Univ. Illinois M cal Center, Chicago, IL, 60680). *In: Prevention and Detec of Cancer. Proceedings of the Third International Sympos on Detection and Prevention of Cancer Held by the Inter tional Study Group for the Detection and Prevention of Ca in New York, April 26 - May 1, 1976.* International St Group for the Detection and Prevention of Cancer. (N York, NY): Vol. 2(Part 1), 2404 pp.; 2019-2028; 1978.

The in vitro effect of the food additive thiodipropionic a (TDPA) on frog (*Rana pipiens*) spinal cord explants was vestigated. The explants were taken from tadpoles at t stages, V and X, and incubated in a soln containing wa and minimum essential medium (9:1). Six days later, addit of 10^{-3} μM TDPA to the culture for 24 hr caused retracti of neuronal fibers. Addition of TDPA for 5 days cau growth and thickening of the fibers, a granular appearan and a large number of fibroblasts. Lowering the TDPA c centration to 10^{-4} μM caused increased thickening a lengthening of the fibers plus increased branching a granularity. At 10^{-1} μM, TDPA caused degeneration a neutrite retraction. The neuronal cultures with TDPA quired no addition of nutrients and showed growth up 40-42 days. Control cultures were unable to grow witho serum, and they grew for only 30-32 days with serum. T neuronal tissue culture system may prove useful in the vitro identification of chemical carcinogens. (43 refs)

78-6118 **Mutagenic Assays with Bis(2-Chloroi propyl)ether (Meeting Abstract).** (Eng) Si mon, V. F. (Stanford Res. Inst., Menlo Park, CA); Hedde L.; Poole, D.; Tardiff, R. *Mutat Res* 53(2): 261-263; 1978. (refs)

78-6119 **Trace Analysis: A Requirement for Toxicolog cal Research with Carcinogens and Hazardou**

bstances. (Eng) Bowman, M. C. (Food and Drug Admin., tl. Center Toxicological Res., Jefferson, AR, 72079). *J As- Off Anal Chem* 61(5): 1253-1262; 1978.

scheme for analyzing an admixture of 13 carcinogens and ated compounds in human urine, wastewater, and environ- ntal surveillance samples (swabs, air filters, etc) is based electron capture gas chromatography of their pentafluoro- pionyl derivatives. (6 refs)

-6120 **Effects of Caffeine on the Frequencies of Chromosomal Aberrations and Sister-Chroma- Exchanges Induced by Mutagenic Agents in Root Tips *Vicia faba* (Meeting Abstract).** (Eng) Sturelid, S. (Dept. netics and Plant Breeding, Royal Agricultural Coll. Swe- n, S-750 07 Uppsala 7, Sweden); Kihlman, B. A. *Mutat Res* (2): 270; 1978. (no refs)

-6121 **Caffeine Inhibition of Liquid-holding Recovery from Ultraviolet-induced Budding Delay in ast Cells.** (Eng) Dawson, P. C. (Dept. Physics, Univ. Vic- ia, Victoria, British Columbia, Canada); Johnson, R. G.; odin, L. J. *Radiat Res* 74(1): 191-198; 1978.

amination of liquid-holding recovery from UV- luced budding delay in yeast cells (*Saccharomyces evisiae*) indicated that addition of 20 mg/ml caffeine to the uid-holding medium completely inhibited the reversal of lding delay. When liquid-holding in caffeine was followed photoreactivation, the budding delay was greatly reduced. ese findings suggest that caffeine interferes with the exci- n of pyrimidine dimers. (20 refs)

-6122 **Evaluation of Possible Mutagenicity of Ginger, Turmeric, Asafoetida, Clove and Cinnamon Ad- nistered Alone and in Combination with Caffeine or eophylline in *Drosophila melanogaster* (Meeting Ab- act).** (Eng) Abraham, S. K. (Sch. Life Sciences, Jawaharlal hru Univ., New Delhi-110057, India); Kesavan, P. C. *tat Res* 53(2): 142; 1978. (no refs)

6123 **Testicular Atrophy and Impaired Spermato- genesis in Rats Fed High Levels of the Methyl- nthines Caffeine, Theobromine, or Theophylline.** (Eng) einberger, M. A. (Div. Pathology, Bureau Foods, Food and ug Admin., Washington, DC, 20204); Friedman, L.; Farb- T. M.; Moreland, F. M.; Peters, E. L.; Gilmore, C. E.; an, M. A. *J Environ Pathol Toxicol* 1(5): 669-688; 1978.

dies were conducted to determine whether simultaneous estion of sodium nitrite and the methylxanthines caffeine (CF), theobromine (TB), or theophylline (TP) would produce lesions similar to those seen in animals treated with other amines and sodium nitrite. Osborne-Mendel male rats (4-6 wk old) were given the methylxanthines at a dietary level of 0.5% for 14-75 wk with and without sodium nitrite (also at 0.5%). The compounds did not produce neoplastic or preneoplastic lesions, but severe bilateral testicular atrophy with aspermatogenesis or oligospermatogenesis occurred in 85%-100% of the rats fed CF and TB. The methylxanthines were fed to male Holtzman rats (4 wk old) at a dietary level of 0.5% for 19 wk to determine whether they would induce testicular atrophy in a second rat strain. The testicular effects were even more pronounced in these rats: CF and TB induced testicular injury in nearly all animals; TP induced severe testicular atrophy in 14% and mild to moderate atrophy in 71%, and it had no effect in only 15% of the rats. There was a significantly reduced number of mitotic cells in testes from the CF-treated group vs those from the TP-treated group. Plasma testosterone concentrations were significantly elevated in the TB group and somewhat elevated in the CF group; plasma cholesterol levels were significantly increased in the CF and TB groups. The toxic effect of CF and TB appeared to be specific for the germinal epithelium of the seminiferous tubules; the Leydig cells in many severely atrophied testes appeared to be hyperplastic. (29 refs)

78-6124 **Modification of DNA by Aflatoxin B_1 Creates Alkali-labile Lesions in DNA at Positions of Guanine and Adenine.** (Eng) D'Andrea, A. D. (Sidney Farber Cancer Inst., Harvard Medical Sch., 44 Binney St., Boston, MA, 02115); Haseltine, W. A. *Proc Natl Acad Sci USA* 75(9): 4120-4124; 1978.

Terminally labeled (^{32}P) DNA fragments of known sequence were used to study the base specificity of modification of DNA by aflatoxin B_1 (AFB_1). The DNA used was a 117- or 168-nucleotide-long DNA fragment that contained the control region, the operator and promoter sequences, of the *lactose* operon. The 168-nucleotide DNA was incubated with 300 μM AFB_1 in the presence of activating enzymes supplied by a crude rat liver extract. This incubation modified the DNA in such a way that subsequent treatment with 1 M piperidine for 30 min or 0.1 M NaOH for 15 min at 90 C resulted in cleavage of the DNA at sites corresponding to the position of guanine residues. The lengths of the cleavage products were the same as those produced by dimethyl sulfate in an alkali-induced reaction. The 117-nucleotide fragment was incubated with 300 μM AFB_1 in the presence of a normal mouse liver extract, and again all possible guanine residues were accessible to modification by AFB_1, but the rate for each individual guanine varied. When the 168-nucleotide fragment was incubated with a high concentration of AFB_1 (1 mM) in the presence of purified rat liver microsomes, deproteinized, and incubated with 1 M piperidine at 90 C, extensive cleavage of DNA was noted, not only at guanine but also adenine residues within the sequence. The DNA products following AFB_1 treatment were identical in length to those

pretreated with Me_2SO_4, a result that suggests that similar mechanisms are involved in the piperidine cleavage of both. (26 refs)

78-6125 **Urinary Excretion of Aflatoxin M_1 after Administration of Aflatoxin B_1 in Sucrose- or Starch-rich Diets.** (Eng) Wise, A. (Regional Mycotoxin Center, Univ. Isfahan, Isfahan, Iran); Suzangar, M.; Messripour, M.; Mohammadi, J. *Br J Nutr* 40(2): 397-401; 1978.

The urinary excretion of aflatoxin M_1 (AFM_1) was compared in two groups of male Sprague-Dawley rats fed a sucrose- or starch-rich diet for 200 days. The diets contained (g/kg): casein (250), corn oil (50), mineral mix (60), vitamin mix (10), and starch or sucrose (630). In addition, 2 mg/kg aflatoxin B_1 was added to the diet. Animals were sacrificed at 75, 145, or 200 days, and livers were examined microscopically. In the last week of life, urine was collected from each rat for 24 hr and analyzed for AFM_1. Although the food intake of both groups was similar, the excretion of AFM_1 (μg/kg/day) was significantly less in sucrose-fed rats (mean value: 1.7 vs 2.3 in starch-fed rats). The livers of sucrose-fed rats were a larger proportion of body weight (49.5 vs 39.1 g/kg), providing more available tissue for metabolism. Therefore, the excretion per gram of liver showed an even larger deficit in sucrose-fed rats, the mean value being 270 vs 560 μg/kg/g liver/day. There was no histological difference between the two groups in the liver slices analyzed. It is suggested that sucrose decreases the activity of the drug-metabolizing enzyme. (14 refs)

78-6126 **Antacids, Bile-Salts, and Colon Cancer (Letter to Editor).** (Eng) Nomura, A. (Japan-Hawaii Cancer Study, Kuakini Medical Center, Honolulu, HI 96817); Stemmermann, G. N.; Glober, G. A. *Lancet* 2(8093): 785; 1978.

Of 8,006 men examined from 1965 to 1968 in the Japan-Hawaii Cancer Study, 345 had had a gastrectomy for gastric or duodenal ulcer. Many of these patients were probably former users of antacids based on aluminum hydroxide. During follow-up, 4 gastrectomy and 94 nongastrectomy men were diagnosed with large bowel cancer. The data do not support the view that aluminum hydroxide increases the risk for colorectal cancer. (1 ref)

78-6127 **Lung Carcinogenesis Induced by Inhaled High-fired Oxides of Beryllium and Plutonium.** (Eng) Sanders, C. L. (Pacific Northwest Lab., Richland, WA, 99352); Cannon, W. C.; Powers, G. J. *Health Phys* 35(2): 193-199; 1978.

The cocarcinogenicity of inhaled, submicron, high-fired $^{239}PuO_2$ and beryllium oxide particles was investigated i 600 Wistar rats. The BeO was calcined at 1000 C and $^{239}PuO_2$ at 750 C. The ultrafilterability of $^{239}PuO_2$ was $<0.$ and it did not increase with time in water suspension. Fe rats were exposed via nose only to BeO and $^{239}PuO_2$ aero for a single period of 30-180 min. There were 12 expo groups: two unexposed control groups (128 rats); t groups exposed to $^{239}PuO_2$ only (184); three groups exp to BeO only (184); and four groups exposed to both ox (119). The amount of oxide in the lung was determine 3-5 rats in each group 24 hr after the single exposure, it ranged from 1.0 to 91 μg for BeO and from 4 to nanocuries (nCi) $^{239}PuO_2$. No unexposed rat developed a l tumor. Only one of the 184 rats exposed to BeO alone d loped a tumor. Lung tumor incidences were 10% at an in alveolar deposition of 5 nCi $^{239}PuO_2$, 37% at 45 nCi, and 5 at 180 nCi. Tumor incidences after exposure to both o particles were 15% at 7.6 nCi $^{239}PuO_2$ and 14 μg BeO, 3 at 76 nCi $^{239}PuO_2$ and 14 μg BeO, 12% at 3.8 nCi ^{239}P and 91 μg BeO, and 58% at 59 nCi $^{239}PuO_2$ and 91 μg B The alveolar clearance of ^{239}Pu decreased and the transl tion of the radionuclide to thoracic lymph nodes incre in rats previously exposed to BeO. It is concluded that p exposure to the BeO did not significantly change the i dence of lung tumors induced by $^{239}PuO_2$, despite the eff of BeO on alveolar clearance. (12 refs)

78-6128 **Mutagenicity of Metal Compounds (Mee Abstract).** (Eng) Kanematsu, K. (Second D Oral Surgery, Gifu Dental Coll., Hosumi, Gifu-ken, Jap Kada, T. *Mutat Res* 53(2): 207-208; 1978. (no refs)

78-6129 **The Mutagenicity of Hexavalent Chromiu Decreased by Microsomal Metabolism.** (E Lofroth, G. (Wallenberg Lab., Univ. Stockholm, S-106 Stockholm, Sweden). *Naturwissenschaften* 65(4): 207-2 1978.

The mutagenicity of hexavalent chromium for *Salmone typhimurium* strains TA1978 and Ta92, as measured with Ames plate-incorporation assay, was decreased by the ac tion of a microsomal activation system containing NA No increase occurred in the absence of the dinucleotide, dicating that it was the main factor contributing to Cr(metabolism in the microsomal system. Oxidation and red tion states did not change when Cr(VI) and NADPH w mixed in aqueous soln, which implied that at least one ac tional factor in the microsomal system was necessary for reaction. (8 refs)

78-6130 **Metabolic Deactivation of Hexavalent Chro um Mutagenicity.** (Eng) Petrilli, F. L. (Inst. I

ne, Univ. Genoa, Via Pastore 1, 16132 Genoa, Italy); De ora, S. *Mutat Res* 54(2): 139-147; 1978.

e mutagenicities of various hexavalent chromium com-unds (sodium dichromate, potassium chromate, chromic id, basic zinc chromate, and basic lead chromate) for *Sal-onella typhimurium* were tested in the presence of rat tissue eparations and human blood components. All hexavalent romium compounds were weakly mutagenic for *S. ty-imurium* his_0 strains and were more mutagenic for strain A100. Addition of the microsomal fraction from rat liver, man RBC lysates, or, to a lesser extent, the S-9 fraction om rat lung reduced the mutagenicity of all divalent romium compounds. Human serum or plasma and the mi-osomal fraction from rat muscle had no effect on the muta-nicities of these compounds. In the presence of the microso-al fraction from rat liver or human RBC lysates, the dition of ascorbic acid, Na_2SO_3, reduced glutathione, ADH, or NADPH prevented hexavalent chromium utagenicity, whereas $KMnO_4$ slightly increased it. The data uld be relevant to the elective localization of chromi-n-induced human lung tumors and could account for the sults of animal carcinogenicity tests, which generally show e development of tumors only at implant sites. (24 refs)

-6131 **A Study of Cancer in Chromate Production Workers.** (Eng) Hayes, R. B. (Johns Hopkins niversity, Baltimore, MD). *Diss Abstr Int B* 39(5): 37-2238; 1978. (no refs)

-6132 **Studies on the Mutagenic Properties of Bleaching Effluents.** (Eng) Ander, P. (Dept. Chemis-y, Box 5604, Swedish Forest Products Res. Lab., S-114 86 ockholm, Sweden); Eriksson, K. E.; Kolar, M. C.; Kring-ad, K.; Rannug, U.; Ramel, C. *Svensk Papperstidning* (14): 454-458; 1977.

mples of industrial effluents from the bleaching of soft-ood kraft pulps were taken from six mills and tested for utagenicity using a streptomycin-dependent strain (Sd-4) *Escherichia coli* and different histidine-requiring mutant rains (TA1535, TA1537, TA1538, TA100) of *Salmonella phimurium*. None of the effluents exhibited any significant utagenic effects or toxicity toward *E. coli*. However, efflu-ts from the chlorination (C) stages exhibited definite muta-nic effects on TA1535 and TA100; concentrated C-stage fluents also had a mutagenic effect on TA1537. A weak utagenic effect was also produced by the hypochloride stage fluent, but the other effluents had little or no mutagenic tivity. The addition of liver microsomes decreased the utagenic activity of the C-stage effluent, indicating a meta-lic detoxification of the mutagen(s). The mutagenic effects the C-stage effluents were almost completely restricted to bstances with low relative molecular mass. Part of the utagenicity remained after ether extraction; the part that was ether-soluble could be destroyed by alkali treatments. The C-stage effluents appear to contain compounds with alkylating and intercalating properties that lead to both base-substitution and frame-shift mutations. (6 refs)

78-6133 **Sarcoma at the Injection Site of Gold Sodium Thiomalate.** (Eng) Payne, B. J. (Dept. Pathology and Toxicology, Smith Kline & French Labs., Philadelphia, PA). *Vet Pathol* 15(Suppl 5): 39-50; 1978.

The local effects on rats following injections of gold sodium thiomalate were studied. Groups of 10 male and 10 female rats were injected in the rear legs with 3, 6, 9, 12, 24, 48, 96, or 192 mg/kg/day, with the right and left legs being injected alternately, every other day. The three highest doses were injected undiluted, the others were diluted with water to make a 2.5% soln. Doses of 48 mg/kg or more produced a considerable local reaction and rats became increasingly belligerent; therefore, rats in dose groups 192, 96, and 48 mg/kg were sacrificed on days 57, 112, and 212, respectively. No tumors were seen in these animals. Doses of 24 mg/kg were generally tolerated without local swelling, although two rats developed hematomas at 7 and 9 mo. Upon sacrifice of the remaining rats of this group (at 357 days) and of the other lower-dose groups (at 514-748 days), a total of nine fibrosarcomas and one rhabdomyosarcoma were found. Unlike the fibrosarcomas, the rhabdomyosarcoma did not invade surrounding muscle. Morphologically, the tumors resembled those found in other studies of the injection of heavy metals into rats. It is suggested that gold be added to the list of heavy metals that produce sarcomas in rats. (10 refs)

78-6134 **Mutagenic, Potentiating and Antimutagenic Activity of Certain Metallic Ions in the Rice Genetic System (Letter to Editor).** (Eng) Reddy, T. P. (Dept. Genetics, Osmania Univ., Hyderabad 500 007, India); Vaidyanath, K. *Curr Sci (Bangalore)* 47(14): 513-515; 1978.

Sets of rice seeds were treated with one of nine metallic salts and/or γ-rays. Seven metals produced chlorophyll mutations in the following order of potency: Ba, Cd (both equal to γ-rays), Cu, Hg, Sr, Fe, and Pb. Mn and Ca were not mutagenic. Sequential treatments suggested that radiation- and metal-induced genetic lesions interacted synergistically in mutation induction. (18 refs)

78-6135 **Cytogenetic and Biochemical Study of Lead-exposed Population (Meeting Abstract).** (Eng) Horvat, D. J. (Inst. Medical Res. and Occupational Health, Zagreb, Yugoslavia); Prpic-Majic, D. *Mutat Res* 53(2): 200-201; 1978. (no refs)

78-6136 Chromosome Analysis of Children Exposed to the Emission of Lead-Smelting Plant (Meeting Abstract). (Eng) Dresp, J. (Institut fur Biologie, Gesellschaft fur Strahlen- und Umweltforschung mbH Munchen, D-8000 Munich, W. Germany); Bauchinger, M.; Schmid, E.; Englert, N. *Mutat Res* 53(2): 181; 1978. (no refs)

78-6137 Manganese Toxicity and Mutagenesis in Two Blue-Green Algae. (Eng) Singh, S. P. (Dept. Botany, Banaras Hindu Univ., Varanasi 221005, India); Kashyap, A. K. *Environ Exp Bot* 18(1): 47-53; 1978.

The toxicity and mutagenicity of manganese were examined in the coccoid blue-green alga *Chroococcus limneticus* and the filamentous blue-green alga *Plectonema boryanum*. *C. limneticus* responded slowly to $MnCl_2$ concentrations <6 mM; at higher concentrations, the survival pattern declined exponentially. Only 1.6% of the cells could form colonies on nutrient agar in the presence of 0.01 M Mn. However, doses causing $<50\%$ lethality (6 mM) were the most efficient at inducing the formation of abnormal cells. Higher doses were more lethal than teratogenic, although all survivors of 9 and 10 mM had abnormalities. The induction of phage- and streptomycin-resistant mutants of *P. boryanum* was investigated at $MnCl_2$ concentrations of 1.0×10^{-6} to 5.0×10^{-4} M. The resistant mutants arose 10-12 days after plating at frequencies ranging from 2.6 to 28.0×10^{-8} for phage resistance and 0.9 to 1.8×10^{-8} for streptomycin resistance. When the algae were exposed to graded concentrations of $MnCl_2$, a sigmoidal pattern of inactivation was observed. The streptomycin-resistant mutants showed increased sensitivity to $MnCl_2$ compared with those of phage-resistant and parent strains. In contrast to *C. limneticus*, microscopic observations revealed no abnormal cell formation or an increase in cell size. When the parent strain of *P. boryanum* was grown in the presence of low concentrations of $MnCl_2$, the phage-resistant mutants did vary in their sensitivity to Mn. The induced frequencies were concluded to be due to the induction of phage-resistant mutants. The max mutant frequencies were approx 10 times that of the background level. Streptomycin-resistant mutants were not induced to a significant level. (22 refs)

78-6138 In Vivo Mutagenesis Investigations of Four GRAS Chemicals (Meeting Abstract). (Eng) Jorgenson, T. A. (Stanford Res. Inst., Menlo Park, CA); Rushbrook, C. J.; Newell, G. W.; Green, S. *Mutat Res* 53(2): 205; 1978. (no refs)

78-6139 Mutagenic Activity of Ethylmercurichloride and Its Disintegration Product Mercury (Meeting Abstract). (Eng) Lekevichus, R. (Dept. Botany and Genetics, State Univ. Vilnius, Lithuanian SSR, USSR); Vijanskaja, T.; Stukiene, R. *Mutat Res* 53(2): 218-219; 197 refs)

78-6140 Chromosome Distribution Studies in Ph Mercury Acetate Exposed Subjects an Age-related Controls. (Eng) Verschaeve, L. (Laborato voor Antropogenetica, Vrije Universiteit Brussel, Brus Belgium); Kirsch-Volders, M.; Hens, L.; Susanne, C. *M Res* 57(3): 335-347; 1978.

The distribution of metaphase chromosomes in the peripl lymphocytes of 16 men exposed to phenyl mercury ac was compared with that in 12 unexposed men. One hun metaphases from both populations were trypsin-banded karyotyped. The relative position of the metaphase chro somes was studied by means of centromere-centromere tances (Δ^2) and centromere-metaphase center distances obtained by computer-aided mathematical transformatic the individual metaphase coordinates. Blood mercury l were within normal limits in both groups: 0 to 3.5 μg the controls and 0 to 5.6 μg/l in the exposed subjects. C genetic analysis showed only a significant increase in hy ploidy in the exposed subjects. There were no translocati However, there were 18 significantly different Δ^2 value tween the two groups. For 12 chromosome groups, the va were greater among the exposed subjects, and for 6 gro the values were smaller for the exposed subjects. Pair 1-1 the only one for which the value in the exposed sub was obviously smaller. The alterations in chromosome di bution due to phenyl mercury acetate were particularly dent among the D-group chromosomes. (18 refs)

78-6141 Nickel-induced Erythrocytosis: Efficacie Nickel Compounds and Susceptibilities of Strains. (Eng) Hopfer, S. M. (Dept. Lab. Medicine, U Connecticut Sch. Medicine, Farmington, CT, 06032); derman, F. W.; Fredrickson, T. N.; Morse, E. E. *Ann Lab Sci* 8(5): 396-402; 1978.

Dusts of nickel subsulfide (αNi_3S_2), nickel sub nide (αNi_3Se_2), nickel monosulfide (βNiS), amorp NiS, and metallic nickel were administered to male Fischer-344 rats intrarenally (ir) to assess relative efficacies of the compounds for erythroc sis (EC) induction. The dusts, which were suspen in 0.2 ml glycerol diluted 1:1 with NaCl soln (mM), were injected into the right kidney. From 4 t wk postinjection, significant differences were obse among the mean blood packed cell volume (PCV) val with the order being $\alpha Ni_3S_2 > \beta NiS > \alpha Ni_3Se_2 > Ni >$ an phous NiS. Crystalline βNiS induced an EC that was alm equal to that for αNi_3S_2, but amorphous NiS did not inc any EC. To study in vitro rates of dissolution of these c pounds, blood samples from Fischer-344 rats were spun equivalent amounts of Ni in the above compounds and cubated. Analyses were performed at 2, 3, 8, and 10 days a

ubation. After 10 days, the concentrations of dissolved Ni erum (μg-atom/ml) were 5.86 amorphous NiS, 3.50 αNi 1.53 αNi_3Se_2, 0.62 βNiS, and 0.38 Ni dust. Six male and female mice of the Fischer-344 (Group H), NIH Black roup I), Wistar-Lewis (Group J), and Long-Evans (Group strains were injected with 5 mg αNi_3S_2 ir to study strain ferences in EC induction. At 2 to 8 wk, significant differes in mean PCV were seen in the following hierarchy: oup H > I > J > K. At 4 wk postinjection, significant ferences were seen in the mean reticulocyte count: Group > I > K > J. It is suggested that induction of EC follow- ir injection could provide a screening technique to test carcinogenicities of Ni compounds. (16 refs)

-6142 **Nickel and Strontium Distribution in Some Mouse Tissues; Passage Through Placenta and ammary Glands.** (Eng) Jacobsen, N. (Dept. Microbiology, ntal Faculty, Univ. Oslo, Blindern, Oslo 3, Norway); Alfm, I.; Jonsen, J. *Res Commun Chem Pathol Pharmacol* (3): 571-584; 1978.

e distribution and retention patterns of nickel and strontiin the soft and hard tissues of female mice were studied. otopes of Sr (0.12 μg/g) and Ni (0.14 μg/g) were injected as the chlorides. The Sr concentration was comparable in liver, kidney, and heart tissue, but brain tissue showed oncentration of one-eighth of those of the other soft tissues. e radioactivity in the calvaria and long bones was eight es greater than that in the liver, and the radioactivity in lower incisors was two to five times greater than that in bones. The distribution in fetal tissues was similar to that the maternal tissue, but the concentrations were reduced. e concentrations in sucklings nursing from a nonradioace female decreased more rapidly than those in sucklings rsing from the biological, radioactive mother. Ni was covered in all soft tissues, the highest concentrations occurg in the kidney and brain, respectively. Ni had no apparent inity for the mineralized tissues, and it was transferred rough the placenta to the progeny; in many tissues, the ogeny had higher concentrations of radioactivity than the other. Ni was also transferred to sucklings through the other's milk. The results indicate that Sr is a bone-seeking neral that forms a hard tissue reservoir, whereas there is prolonged retention of Ni in mineralized tissue. (16 refs)

-6143 **The Induction of Malignant Tumors in Rats by Nickel-containing Aerosols.** (Rus) Saknyn, A. (Res. Inst. Vocational Hygiene and Occupational Dises, Sverdlovsk, USSR); Blokhin, V. A. *Vopr Onkol* 24(4): -48; 1978.

e results of a toxicologic experiment on the long-term efts of nickel-containing industrial dusts (NCID) are prented. Random-bred albino rats were (1) subjected to daily halations of NCID (av content of dust in the chamber, 70 mg/m³), 5 hr/day, 5x/wk, for 6 mo; (2) inoculated ip with NCID soln (90-150 mg/1.5 ml); or (3) administered NCID soln intratracheally (20-40 mg/0.6 ml). Within 6-15 mo of ip NCID administration, 6/39 rats developed sarcomas (3 reticulosarcomas of the abdominal lymph nodes, 3 fibrosarcomas of the abdominal wall). After ip and intratracheal administration of NCID, 1/5 and 1/26 rats, respectively, developed lung cancer. The latent period of lung tumor development in both cases was 17 mo. (12 refs)

78-6144 **Evaluation of Tris (2,3-dibromopropyl)phosphate for Mutagenic and Transforming Activity in a Battery of Test Systems (Meeting Abstract).** (Eng) Brusick, D. (Dept. Genetics, Litton Bionetics, Inc., Kensington, MD, 20795); Matheson, D.; Bakshi, K. *Mutat Res* 53(2): 160; 1978. (no refs)

78-6145 **Test of O,O-Dimethyl(1-hydroxy-2,2,2-trichloroethyl)phosphonate (Trichlorofon) for Carcinogenic Activity in Rats Following Oral (Esophageal-Gastric Intubation) and Intraperitoneal Application.** (Rus) Teichmann, B. (Zentralinstitut fur Krebsforschung, Akademie der Wissenschaften der DDR, Lindenberger Weg 80, DDR-1115 Berlin-Buch, E. Germany); Hauschild, F.; Eckelmann, A. *Arch Geschwulstforsch* 48(2): 112-119; 1978.

The carcinogenicity of O,O-dimethyl(1-hydroxy-2,2,2-trichloroethyl)phosphonate (Trichlorofon) was examined in albino rats following po (esophageal-gastric intubation: 22 mg/kg 2x/wk) and ip (12 mg/kg 2x/wk) administration. Controls were given po or ip NaCl soln. All animals were treated for 90 wk; the experiment was terminated at 118 wk. There was no statistically significant difference in tumor incidence between treated and control animals by either route of application. (41 refs)

78-6146 **Selenium and Cancer: Effects of Selenium and of the Diet on the Genesis of Spontaneous Mammary Tumors in Virgin Inbred Female C_3H/St Mice.** (Eng) Schrauzer, G. N. (Dept. Chemistry, Univ. California at San Diego, La Jolla, CA, 92093); White, D. A.; Schneider, C. J. *Bioinorg Chem* 8(5): 387-396; 1978.

The efficacy of dietary selenium in reducing the incidence of spontaneous mammary tumors was studied in inbred female C_3/St mice, which show an 80% to 100% incidence of spontaneous tumor development. The animals were maintained on a basal diet (main source of protein, fishmeal) containing 0.45 ppm Se. Se supplementation was started at 2 mo of age and continued throughout life. Mice receiving 0.1 and 0.5 ppm Se in the drinking water gained wt faster than those receiving no Se in the drinking water (controls) or those receiving 1.0 ppm; the difference was significant at 1 yr. After

24 mo, tumor incidence in the control group was 42%, which was significantly lower than that in mice fed a diet containing 0.15 ppm Se, with meat and dried skimmed milk as major source of protein (80%-100%, previous study). The incidence of tumors declined progressively and the age at first tumor appearance increased progressively with increasing Se supplementation. Tumor growth rates did not differ significantly among the groups. A higher frequency of mesentery tumors was observed among controls (5/7) than among Se-supplemented animals (3/14). There was no histological evidence of liver damage in any group. The data suggest that a human diet rich in Se-containing seafoods and cereals could lower the cancer risk compared with a predominantly meat-based diet. (9 refs)

78-6147 **Mutagenicity of Heavy Metals (Meeting Abstract).** (Eng) Deknudt, G. (Dept. Radiobiology, Lab. Genetics, S.C.K.-C.E.N., B-2400 Mol, Belgium). *Mutat Res* 53(2): 176; 1978. (no refs)

78-6148 **Relation Between Gastric Cancer Mortality Rate and Amounts of Zn in Rice in Nara Prefecture, Japan.** (Jpn) Ikeda, K. (Dept. Hygiene, Nara Medical Univ., Kashiwara-shi, Nara Prefecture 634, Japan). *J Nara Med Assoc* 28(6): 909-916; 1977.

The relationship between gastric cancer mortality and zinc levels in the rice was determined for Nara Prefecture, Japan. This region has the highest gastric cancer mortality rate in Japan, although the rate has been declining in recent years; in one of its districts (Uda), however, the rate has been rising in the elderly. Unhulled rice from 129 areas in Nara Prefecture was analyzed for trace metals. Zn, Fe, and Cu levels were higher than the av values for the nation, and that of Ca was lower. The coefficient of variation was higher for Fe, Cu, and Cd than for Mg, Zn, and Ca. The distribution curves for Mg, Ca, and Fe skewed to the left, that of Zn had two peaks. The ratio of the metal concentration in unhulled and hulled rice was 0.08 for Mg, 0.54 for Zn, and 0.90 for Ca. Classification according to district showed that Uda had higher levels of Mg, Zn, and Ca in its rice than the other districts. Apparently, the high level of Zn in rice is related to the high gastric mortality rate. (9 refs)

78-6149 **Short-term Toxicity Study of Chocolate Brown HT in Pigs.** (Eng) Hendy, R. J. (British Industrial Biological Res. Assoc., Woodmansterne Road, Carshalton, Surrey SM5 4DS, England); Butterworth, K. R.; Gaunt, I. F.; Hooson, J.; Grasso, P. *Toxicology* 11(2): 189-192; 1978.

The toxicity of Chocolate Brown HT a food coloring agent, was studied in 10-wk-old male and female Large White pigs. The coloring was incorporated in the diet for 13 wk at a dose level of 0, 5, 20, or 100 mg/kg/day. There were no abnorm ties in the condition or appearance of the pigs, body wt g absolute organ wts, or urine. Feces of pigs given mg/kg/day were dark brown and occasionally maroon in or. Significantly reduced Hb concentrations in all group treated male and elevated WBC counts in a single female a single male were not considered to be related to treatm with Chocolate Brown HT. Scattered significant differer in relative organ wts between control and treated pigs w also considered to be unrelated to Chocolate Brown HT. the basis of these results, an acceptable daily intake of Cho late Brown HT for man would be 1 mg/kg or about 70 for an adult. (6 refs)

78-6150 **The Mutagenicity of a Sauna Pine Scent Pr uct in *Salmonella typhimurium* and *charomyces cerevisiae* (Meeting Abstract).** (Eng) De Mar D. M. (Dept. Biological Sciences, Illinois State Univ., N mal, IL). *Mutat Res* 53(2): 178; 1978. (no refs)

78-6151 **Chromosomal Damage and Hair Dyes (2 Lett to Editor).** (Eng) Feinstein, A. R. (Dept. Me cine, Yale Univ. Sch. Medicine, New Haven, CT, 065 Kirkland, D. J.; Lawler, S. D.; Venitt, S. *Lancet* 2(80 627-629; 1978.

Criticisms concerning an investigation of the possible c cinogenicity of hair dyes are listed, as are, in a subsequ letter, the replies to these criticisms. In the reply, it is repe ed that an excess of chromosome damage (over that in controls) was found in a group of 60 professional hair-dye However, the excess was not definitive. (7 refs)

78-6152 **On the Mutagenicity of Some Azo-Dyes (Me ing Abstract).** (Eng) Busk, L. (Toxicology La Swedish Natl. Food Admin., Box 622, S-751 26 Uppsa Sweden); Albanus, L. *Mutat Res* 53(2): 161; 1978. (no re

78-6153 **Investigations into Genetic Activity of Fo Dyes (Meeting Abstract).** (Eng) Smith, R. (Dept. Biological Sciences, Portsmouth Polytechnic, Po smouth, England); Combes, R. D. *Mutat Res* 53(2): 2 1978. (no refs)

78-6154 **Correlation Between the Carcinogenicity of C ganic Substances and Their Spectral Charact istics.** (Eng) Veljkovic, V. (Boris Kidric Inst. Nucle Sciences, Lab. Theoretical Physics, P.O. Box 522, 11001 B grade, Yugoslavia); Lalovic, D. I. *Experientia* 34(1 1342-1343; 1978.

ce the UV radiation that is most effective in inducing can- lies in the region 233-278 nanometers (nm), the UV ab- ption spectra of chemical carcinogens were analyzed to ermine whether they have peaks in this spectral region and ether they differ in this respect from noncarcinogens. A ong correlation was found between the UV spectral char- eristics and carcinogenicity of a variety of organic sub- nces. The organic carcinogens had an absorption peak(s) he 206- to 248-nm region. These findings and those from ceding work resulted in the formulation of the following nciple: if an organic chemical has an av quasi-valence mber <3.20 and if its spectrum shows an absorption k(s) in the wavelength region 206-248 nm, it should be sidered carcinogenic. This rule was fulfilled for 91% of chemicals tested. A mechanism of carcinogenesis is posed that assumes that cancer associated-DNA is a cked part of normal cell DNA. The most important step carcinogenesis is deblocking of cancer-associated DNA. e deblocking mechanism is independent of the nature of carcinogenic agent and must be due to some characteristic rgy features. (6 refs)

-6155 **Effects of Harman and Norharman on Spontaneous and Ultraviolet Light-induced Mutagenesis in Cultured Chinese Hamster Cells.** (Eng) Chang, C. (Dept. Human Development, Coll. Human Medicine, Mi- gan State Univ., East Lansing, MI, 48824); Castellazzi, ; Glover, T. W.; Trosko, J. E. *Cancer Res* 38(12): 27-4533; 1978.

e effects of nontoxic concentrations of two nonmutagenic carboline derivatives, harman (HM) and norharman HM), on DNA repair and mutagenesis were studied in ltured Chinese hamster (V79) cells. Cytotoxicity studies owed that the colony-forming ability of the cells was unaf- ted by 5 μg/ml HM and decreased to only 85% by 10 μ/ ; 20 μg/ml completely eliminated colony-forming ability, ereas this dosage of NHM inhibited plating efficiency to ly 65%. The survival of UV- or x-ray-damaged V79 cells posed to 30 or 50 μM HM was significantly reduced com- red with cells not treated with HM, and the effect was ncentration-dependent. The effect was not detectable at 10 M. The unscheduled DNA synthesis induced by UV light 00-900 R) was slightly, but consistently, inhibited by HM, t normal DNA synthesis was unaffected. The frequency spontaneous or UV light-induced ouabain-resistant or hioguanine-resistant mutations was reduced by HM. The ect of HM on survival and mutagenesis was greater than at of NHM and was detected primarily when cells were posed to HM immediately after UV irradiation. The muta- n frequency was reduced significantly by 28 μM NH at 3.5 days after UV irradiation and by 30 μM at 0-1.5 days er irradiation. The data indicate that HM decreases the pacity of V79 cells to repair DNA damage and fix muta- ns, possibly because of its intercalation properties. (28 refs)

-6156 **Perspective in Chronobiology of Air Pollution.** (Eng) Stupfel, M. (French Natl. Inst. Health (INSERM), 101 rue de Tolbiac, Paris 75013, France); Halberg, F.; Mordelet-Dambrine, M.; Magnier, M. *Chronobiologia* 4(4): 333-351; 1978.

Chronobiological experiments with rodents that determine how cycles in air pollutant emissions synchronize, reinforce, or interfere with the internal or endogenous rhythms characteristic of human physiology or physiopathology are reviewed. (56 refs)

78-6157 **The Mutagenicity of a Dinitro-o-cresol-containing Pesticide.** (Hun) Nehez, M. (Kozegeszsegugyi es Jarvanytani Intezet, SZOTE, Szeged, Hungary); Selypes, A.; Paldy, A. *Egeszsegtudomany* 21(3): 237-243; 1978.

The mutagenicity of Krezonit E, which contains 50% dinitro-o-cresol (DNOC) as the active agent, was studied in vitro in normal human WBC cultures and in vivo in bone marrow cell cultures of treated male albino mice. The numbers of human WBC with chromosome aberrations increased with DNOC concentration, from 113/200 at 0.02 μg/ml to 125/196 at 0.2 μg/ml and to 129/200 at 2 μg/ml. Chromatid-type aberrations accounted for 35.7% of all aberrations, and their frequency was DNOC concentration-dependent; chromosome-type aberrations accounted for 25%, and their frequency was DNOC concentration-independent. Numerical aberrations occurred at a frequency of 0.3%. The spontaneous aberration rate was 2.5%. In mice, the number of cells with chromosome aberrations was (a) 75/100 in bone marrow cultures from those treated with a single ip injection of DNOC (20 mg/kg) and (b) 76-95/100 in those treated with five ip injections of 1, 5, or 10 mg/kg on days 1, 3, 5, 7, and 9 before sacrifice on day 10, which indicates that the mutagenicity of DNOC is higher after subacute treatment. Most of the aberrations were of the chromosome type; labile aberrations accounted for 4%-7%, stable aberrations for 68%-85%. Chromatid-type aberrations accounted for 1%-10%. The spontaneous aberration frequency was 1/100. The findings show that DNOC is mutagenic. (24 refs)

78-6158 **Evaluation of Organic Extracts of Drinking Water by Bacterial Mutagenesis (Meeting Abstract).** (Eng) Loper, J. C. (Dept. Microbiology, Univ. Cincinnati Medical Center, Cincinnati, OH); Schoeny, R. S.; Tardiff, R. G. *Mutat Res* 53(2): 223-224; 1978. (2 refs)

78-6159 **Galactose-Resistant Forward Mutation Induction in *E. coli* K-12 and *S. typhimurium* galE or galU Strains by Environmental Mutagens (Meeting Abstract).** (Eng) Clarke, C. H. (Sch. Biological Sciences, Univ. East Anglia, Norwich, NR4 4TJ, England); Shankel, D. M. *Mutat Res* 53(2): 168; 1978. (no refs)

78-6160 **Co-operative Mutagenic Actions of Bisulfite and Nitrogen Nucleophiles (Meeting Abstract).** (Eng) Hayatsu, H. (Faculty Pharmaceutical Sciences, Univ. Tokyo, Bunkyo-ku, Tokyo 113, Japan). *Mutat Res* 53(2): 197; 1978. (1 ref)

78-6161 **The Detection of Mutation in Human Diploid Fibroblasts after Mutagen Treatment Using Non-selective Cloning and Enzyme Electrophoresis.** (Eng) Nelson, R. L. (Dept. Surgery, Univ. Illinois Hosp., P.O. Box 6998, Chicago, IL, 60680); Harris, H. *Mutat Res* 50(2): 277-283; 1978.

Human diploid fibroblasts from a 21-yr-old man (RM3), an 11-yr-old boy (FS1), and a male infant (PM1) were exposed to ethyl methanesulfonate (EMS): 400-1,100 μg/ml and examined for mutation using nonselective cloning and enzyme electrophoresis. RM3 cultures had three doses of EMS, and between each dose the cells were cultured in fresh medium. The RM3 cells maintained a normal morphology and a reasonable incidence of survivors with doses of EMS up to 1,100 μg/ml. PM1 cells, however, died at levels of EMS > 400 μg/ml. The FS1 culture was intermediate in its sensitivity to EMS. Clones that were isolated following mutagen treatment were analyzed by starch-gel electrophoresis. Two mutants were identified: an electrophoretic variant of peptidase D (PEPD) was observed in an FS1 clone and a phenotypic alteration involving phosphoglucomutase (PGM_1) was found in an RM3 clone. (8 refs)

78-6162 **The Evaluation of Sixteen Carcinogens in the Rat Using the Micronucleus Test.** (Eng) Trzos, R. J. (Upjohn Co., 301 Henrietta St., Kalamazoo, MI, 49001); Petzold, G. L.; Brunden, M. N.; Swenberg, J. A. *Mutat Res* 58(1): 79-86; 1978.

The ability of the micronucleus test to detect clastogenic promutagens/procarcinogens was evaluated using 16 known carcinogens, 15 of which require tissue-specific metabolic activation. Groups of three male TUC(SD) spf (Sprague-Dawley) rats were administered a single ip injection of one of three doses/compound. The direct-acting mutagen ethyl methanesulfonate and the promutagens/procarcinogens cyclophosphamide and 4-nitroquinoline 1-oxide produced statistically significant dose-response increases in the number of micronucleated polychromatophilic RBC (MP-RBC). A marginally significant dose response was exhibited by dimethylnitrosamine. Aflatoxin B_1 significantly increased the number of MP-RBC at two doses, but a dose-response relationship was not found. The other agents, 2-acetylaminofluorene, 4-aminobiphenyl, benzidine, diethylnitrosamine, 9,10-dimethylbenzanthracene, 1,2-dimethylhydrazine, ethyl carbamate, β-naphthylamine, ethionine, hexametapol, and metronidazole, did not increase the number of micronuclei significantly. Thus, the micronucleus test appears to lack the sensitivity for detecting procarcinogen/promutagens tha quire tissue-specific metabolic activation or are rapidly i tivated. (22 refs)

78-6163 **Mutagenicity of Some Environmental Ch cals in Salmonella Test Systems without crosomal Activation (Meeting Abstract).** (Eng) Adams, J (Regional Science Teaching Center, Regional Staff Deve ment Center, Graduate Sch., Notre Dame of Marbel C Koronadal, South Cotabato 9708, Philippines). *Mutat* 53(2): 142-143; 1978. (no refs)

78-6164 **Comparison of Toxicity and Mutagenicity Butyl Methanesulfonate among Human L phoblast Lines.** (Eng) Slapikoff, S. A. (Dept. Biology, T Univ., Medford, MA, 02155); Andon, B. M.; Thilly, W. *Mutat Res* 54(2): 193-196; 1978.

A comparison was made of the toxicity and mutagenicity butyl methanesulfonate (BMS) among four diploid hun lymphoblast lines: MIT-2, from a female mononucleosis tient; GM 130, from a normal man; MGL8B-2, a clo derivative of line MGL8 isolated from a normal man; WI-L2, from a man with hereditary spherocytosis. Each was exposed to 0-3 mM BMS for 24 hr. A period of ≥12 d was allowed for expression of the mutant phenotype, lack hypoxanthine-guanine phosphoribosyltransferase activ The mutant fraction was determined by soft-agar plating the cultures in the presence and absence of 10 μg/ml 6- oguanine. BMS was toxic and mutagenic to lines MGL8 MIT-2, and WI-L2, particularly to the latter two lines. contrast, GM 130 cells demonstrated almost complete res ance to these effects of BMS, even at the highest concent tion tested. Line GM 130 was also highly resistant to the to and mutagenic effects of methylnitrosourea and methyl tronitrosoguanidine, at concentrations highly toxic mutagenic to line MIT-2. The reason(s) for the resistance line GM 130 is not known. (9 refs)

78-6165 **The Potential Carcinogenicity of Met Fluorosulphonate (CH_3OSO_2F; Magic M thyl).** (Eng) Ashby, J. (Central Toxicology Lab., Imper Chemical Industries Ltd., Alderley Park, Macclesfield, Ch shire, England); Anderson, D.; Styles, J. A. *Mutat Res* 51(285-287; 1978.

The potential carcinogenicity of methyl fluorosulfon (MFS) was evaluated in two short-term in vitro tests, t Salmonella reverse mutation assay and in a cell transform tion assay. In the former, MFS was mutagenic to Salmone strain TA1538 in a dose-dependent manner at concentratio up to 500 μg/plate in the absence of a metabolizing syste It produced a max of 140 revertants/plate (vs 20/plate

trol cultures). MFS resulted in 100% lethality of baby ıster kidney 21/C13 cells at a concentration of 2.5 μg/ml, ɔse that also induced a max of 900 transformants/10^6 sur- ɔrs (vs 60/10^6 in control cultures). Both cell survival and ısformation induction were dose-dependent. The chemical ctivity of MFS and the results of these assays are consist- with this compound being a possible carcinogen. Howev- most, if not all, chemical alkylating agents are probably able of producing positive results in in vitro assays, and they may not all prove to be carcinogenic in vivo. (9 refs)

-6166 **Carcinogenicity and Mutagenicity of 47 Heteropolycyclic Compounds (Meeting Ab-** ıct). (Eng) Glatt, H. R. (Pharmakologisches Institut der iversitat, D6500 Mainz, W. Germany); Schwind, H.; Zaj- a, F.; Jacquignon, P. C.; Oesch, F. *Mutat Res* 53(2): -193; 1978. (no refs)

-6167 **Mutagenicity of Chlorinated Cyclopentadienes Due to Metabolic Activation (Meeting Ab-** act). (Eng) Goggelmann, W. (Gesellschaft fur Strahlenfor- ıung, Ingolstadter Landstrasse 1, 8042 Neuherberg, W. rmany); Greim, H.; Bonse, G.; Henschler, D. *Mutat Res* (2): 193-194; 1978. (no refs)

-6168 **Asbestos Exposure and Related Neoplasia. The 28 Year Experience of a Major Urban Hospital.** ng) Hasan, F. M. (Div. Respiratory Sciences, Arizona ealth Sciences Center, Univ. Arizona, Tucson, AZ, 85724); ash, G.; Kazemi, H. *Am J Med* 65(4): 649-654; 1978.

rty-nine asbestosis patients were seen at Massachusetts eneral Hospital between 1945 and 1972, 30 of whom also d cancer: 17 mesothelioma, 12 lung cancer (6 adenocar- ıoma), and 1 prostate cancer. Only four asbestosis cases ere diagnosed before 1960, and the diagnosis has been made ith increasing frequency since then. Forty-eight patients d been exposed occupationally to asbestos, and 38 of these tients had a history of significant exposure in naval ship- rds. One asbestosis patient with adenocarcinoma had no own history of exposure. The mean age of the patients was 7.7 yr, 45/49 were men, and only 4 were nonsmokers. In 7 patients, the exposure to asbestos was >15 yr. Most pa- ents with brief exposure had an associated neoplasm, and ey presented with symptoms related to the tumor and not sbestosis. In 9/12 cancer patients who gave a history of ex- osure of <5 yr, the neoplasm was mesothelioma. Unlike atients with uncomplicated asbestosis who often had worked ith asbestos until the time of their illness, in patients with related neoplasm there was a long interval between last xposure and emergence of symptoms. The mean latent peri- d between onset of exposure and diagnosis of asbestos-relat- d neoplasia was 26.3 yr. When pathologic data on 20 pa- tients with autopsy studies were correlated with premortem roentgenologic changes, the latter seemed to underestimate the underlying disease. (26 refs)

78-6169 **Aryl Hydrocarbon Hydroxylase in Asbestos Workers.** (Eng) Naseem, S. M. (Channing Lab., Dept. Medicine, Harvard Medical Sch., 180 Longwood Ave., Boston, MA, 02115); Tishler, P. V.; Anderson, H. A.; Selikoff, I. J. *Am Rev Respir Dis* 118(4): 693-700; 1978.

The hypothesis that significant asbestos exposure may lead not only to long-term pulmonary accumulation of aromatic hydrocarbons, but also to increased inducibility (Ind) of aryl hydrocarbon hydroxylase (AHH) was tested by investigating lymphoblast AHH Ind in 47 asbestos workers (all men) and 31 control subjects (11 men, 20 women). Controls included 20 relatives of the exposed subjects, 12 of whom were spouses. Mean Ind [3-methylcholanthrene (3-mc)-dibenz(a,h)anthracene (DBA)-induced divided by basal enzyme activity] was significantly greater in the asbestos workers than in controls. The estimated change in the mean value of MC Ind was 0.88, that of DBA Ind 1.59. The increased Ind appeared to result almost exclusively from an increase in induced enzyme activity; there was little change in basal enzyme activity. Factors such as age, smoking status, year of first exposure, yield of lymphoblasts in culture, and blastogenesis rate (measured by incorporation of ^{3}H-thymidine into nucleic acid) had no effect on differences in AHH Ind ratios. The fact that spouses with potential household exposure did not have increased AHH Ind suggests that some minimal dose of asbestos is essential for this effect. Increased AHH Ind may bear some relation to the previously determined greatly increased risk ($\geq$90-fold) of bronchogenic carcinoma in asbestos workers who smoked cigarettes vs workers who did not smoke. (47 refs)

78-6170 **Cytogenetic Effects of the Gaseous Phase of Cigarette Smoke on Root-Tip Cells of *Allium sativum* L.** (Eng) Pandey, K. N. (T. H. Morgan Sch. Biological Sciences, Univ. Kentucky, Lexington, KY, 40506); Benner, J. F.; Sabharwal, P. S. *Environ Exp Bot* 18(1): 67-75; 1978.

The cytogenetic effects of the gaseous phase of cigarette smoke from five types of experimental cigarettes on the root tip cells of garlic, *Allium sativum* L., were determined. The root tips were exposed to 1, 2, 3, 4, 5, 10, 15, or 20 35-ml puffs of smoke at 7-min intervals. Chromosome abnormalities in the form of breakages (mostly fragments), bridges, lags, stickiness, and differential condensation were observed. Multinucleate cells, polyploid cells, and multipolar mitotic divisions were also noted. In general, the percentage of abnormalities increased when root tips were exposed to higher numbers of puffs. The mitotic index increased at low levels of smoke exposure, but it declined sharply at higher levels

of exposure. An analysis of variance indicated that the results were highly significant for cigarette types and exposure times with respect to the mitotic index as well as the total number of abnormally dividing cells. (24 refs)

78-6171 **Analysis of a Tumor-inhibiting Fraction of Tobacco Smoke Condensate.** (Eng) Chamberlain, W. J. (Tobacco Lab., Science and Education Admin., Federal Reserve, U.S. Dept. Agriculture, P.O. Box 5677, Athens, GA, 30604); Snook, M. E.; Haeberer, A. F. *J Anal Toxicol* 2(4): 138-140; 1978.

A tumor-inhibiting fraction of cigarette smoke condensate containing ether-soluble neutrals was partially characterized by gel filtration and gas chromatography. In addition to solanesol, sterols, and other neutral oxygenated compounds such as acetophenones and fluorenones, this fraction contained 1,3-indandione, a compound new to cigarette smoke. (10 refs)

78-6172 **A Comparison of Short Term Bioassay Results with Carcinogenicity of Experimental Cigarettes.** (Eng) Basrur, P. K. (Dept. Biomedical Sciences, Univ. Guelph, Guelph, Ontario, Canada); McClure, S.; Zilkey, B. *In: Prevention and Detection of Cancer. Proceedings of the Third International Symposium on Detection and Prevention of Cancer Held by the International Study Group for the Detection and Prevention of Cancer in New York, April 26 - May 1, 1976.* International Study Group for the Detection and Prevention of Cancer. (New York, NY): Vol. 2(Part 1), 2404 pp.; 2041-2048; 1978.

Four experimental cigarettes with known tumor induction potential in long-term tests were examined in two short-term bioassays, the *Salmonella typhimurium* mutagenicity assay and the mouse skin response test, and the results were compared. In the mutagenicity assay, rankings using condensates and smoke on a concentration basis were similar for the extremes, but the intermediate rankings were reversed. The mutagenicity ranks of condensate calculated on a per cigarette basis paralleled the total tumor potency trend established by long-term tests. The mutagenicity values obtained for fresh smoke on a per cigarette basis did not follow the same pattern. All of the tests, including the sebaceous gland suppression response in mouse skin with 10% condensates, detected the same cigarette as the most active. The epidermal hyperplasia response in mouse skin did not distinguish the extremes with either of the two concentrations of condensate (10% and 20%) used. It is concluded that the epidermal hyperplasia response, assumed to be a measure of the promoters in cigarette smoke, was not helpful in rating cigarettes whereas the sebaceous gland suppression response, which reflects the tumor initiator levels, and the mutagenicity response may be used as indices of biological insult correlated with the tumor-inducing potency of cigarettes. (8 refs)

78-6173 **In Vitro Transformation of Hamster Emb Cells by Betel Tobacco Extracts.** (Eng) Um wa, K. (Dept. Experimental Pathology, Cancer Inst., 1-3 Kami-Ikebukuro, Toshima-ku, Tokyo 170, Japan); Tak ma, S.; Fujie, S.; Matsushima, T.; Sugimura, T. *Toxicol* 2(4): 243-246; 1978.

The transforming effects of the ethanol and ethyl acetate tracts of betel tobacco on cryopreserved hamster embryo were studied. The ethanol extract induced one transfor colony at 100 μg/ml, and the ethyl acetate extract indu two transformed colonies at 5 μg/ml and two colonies at μg/ml. The positive results in this assay were significan that no transformation was observed in control cultures. ethyl acetate extract of betel tobacco may contain carcino ic principle(s) of betel. (5 refs)

78-6174 **Aryl Hydrocarbon Hydroxylase Induction Human Lymphocytes and Sensitivity of Sev Hematopoietic Parameters to Cigarette Smoking.** (E Shultz, T. D. (Res. Section., Mountain States Tumor I Boise, ID, 83702); Smith, C. E.; Steuart, C. D. *In: Preven and Detection of Cancer. Proceedings of the Third Inte tional Symposium on Detection and Prevention of Cancer by the International Study Group for the Detection and vention of Cancer in New York, April 26 - May 1, 1976.* In national Study Group for the Detection and Prevention Cancer. (New York, NY): Vol. 2(Part 1), 2404 1677-1687; 1978.

Aryl hydrocarbon hydroxylase (AHH) activity was assa in cultured lymphocytes obtained from 30 healthy smok and 30 healthy nonsmokers. Total WBC, Hb, and hemato values were also compared for the smokers and nonsmok Smokers had significantly higher total WBC and Hb le than nonsmokers; the hematocrit differences were not sig cant. Mean AHH activity was twice as high in smokers (0. unit) as in nonsmokers (0.058 unit). There was a nega correlation between the number of cigarettes consumed day and the level of AHH induction. Arbitrary low, in mediate, and high subgroups within the smoker and no moker populations suggested a trimodal distribution of absolute AHH levels, but the significance of this relations could not be determined because of the small number of dividuals in each subgroup. The lack of a correlation betw the number of cigarettes consumed per day and AHH ind tion suggests that the latter is under genetic control rat than being a quantitative response to polycyclic hydroc bons. (50 refs)

78-6175 **Metabolic α-Hydroxylation of the Tobacco-s cific Carcinogen, N′-Nitrosonornicotine.** (E Chen, C. B. (Div. Environmental Carcinogenesis, Nay Dana Inst. Disease Prevention, American Health Foun

n, Valhalla, NY, 10595); Hecht, S. S.; Hoffmann, D. *Can- Res* 38(11, part 1): 3639-3645; 1978.

e metabolism of N′-nitrosonornicotine (NNN), a carcino- n that occurs in cigarette and cigar tobacco, mainstream d sidestream cigarette and cigar smoke, chewing tobacco, d snuff, was investigated in male F-344 rats, with emphasis the α-hydroxylation pathway. Since α-hydroxynitrosa- nes are unstable, the model compounds 2′- and 5′-ace- xy-NNN were hydrolyzed to determine the decomposition oducts of 2′- and 5′-hydroxy-NNN. The major products 2′-acetoxy-NNN were myosmine (MM: 50%-60%) and ıydroxy-1-(3-pyridyl)-1-butanone (HPB: 5%-10%), that 5′-acetoxy-NNN was 2-hydroxy-5-(3-pyridyl-tetrahy- ofuran (HPTHF: 60%-70%). Hydrolysis of a third model mpound, 4-(N-carbethoxy-N-nitrosamino)-1-(3-pyridyl)- utanone, also gave HPB (50%-60%). These results sup- rt the intermediate role of electrophilic diazohydroxides d/or carbonium ions in the decomposition of 2′- and 5′- droxy-NNN. These electrophiles may be active forms of NN, since all three model compounds were mutagenic to- ard *Salmonella typhimurium* TA100 without enzymatic ac- ation. Upon incubation of ^{14}C-NNN with rat liver mi- osomes, O_2, and NADPH, HPB and HPTHF were oduced as the 2,4-dinitrophenylhydrazone derivatives. M was formed in incubation mixtures analyzed without rivative formation. When rats were inoculated with 87.3 g ^{14}C-NNN sc, 73%-85% of the dose appeared in the 48-hr ine. The major metabolites were 4-(3-pyridyl)-4-oxobutyric id, 4-hydroxy-4-(3-pyridyl)butyric acid, and 5-(3-pyridyl)- trahydrofuran-2-one, the oxidation products of HPB and PTHF. The results are consistent with the hypothesis that NN is activated by α-hydroxylation. (36 refs)

3-6176 **Chemical Studies on Tobacco Smoke. LI: Studies on Non-volatile Nitrosamines in Tobacco.** Eng) Hecht, S. S. (Naylor Dana Inst. Disease Prevention, merican Health Foundation, Dana Road, Valhalla, NY, 0595); Chen, C. B.; Dong, M.; Ornaf, R. M.; Hoffmann, D.; so, T. C. *Beitr Tabakforsch* 9(1): 1-6; 1977.

he isolation of the Z (syn) and E (anti) isomers of N′- itrosonornicotine (NNN) from tobacco, the influence of ıring and stalk position on NNN levels in tobacco, and the nthesis of two new nitrosamines that may also be present ı tobacco are described. Commercial and noncommercial Burley, Bright) tobacco samples were used. The E/Z ratio ı fine-cut chewing tobacco was determined by high-pressure quid chromatography to be similar to that observed in soln : similar pH (7.6) and temperature (25 C). The interconver- on rate was first-order and reversible, and it increased at wer pH. NNN was not detected (detection limit, 40 nano- rams/g dry tobacco) in uncured tobacco. In tobacco grown n high N fertilization, the presence of NNN was confirmed eginning at the half-cured stage. NNN levels were higher ı the high-N than in the low-N-fertilized samples, in which NNN was detected only after complete curing. No significant correlation was observed between stalk position and NNN levels in one variety of Bright tobacco. 4-(N-methyl-N-nitrosamino)-1-(3-pyridyl)-butanal and 4-(N-methyl-N-nitrosamino)-1-(3-pyridyl)-1-butanone, two additional nitrosamines that, theoretically, could also arise from nicotine were synthesized, and a detailed description of the process is given. (21 refs)

78-6177 **Long-Term Fate of [^{14}C]Nicotine in the Mouse: Retention in the Bronchi, Melanin-Containing Tissues and Urinary Bladder Wall.** (Eng) Szuts, T. (Dept. Toxicology, Univ. Uppsala, Biomedical Center, Box 573, S-751 23 Uppsala, Sweden); Olsson, S.; Lindquist, N. G.; Ullberg, S.; Pilotti, A.; Enzell, C. *Toxicology* 10(3): 207-220; 1978.

The long-term fate of N-methyl-^{14}C- and 2′-^{14}C-labeled nicotine in pigmented C57BL and albino NMRI mice was studied using whole-body autoradiography, liquid scintillation counting, and thin-layer chromatography (TLC). Thirty days after injection, N-methyl-^{14}C-nicotine persisted in the pigmented uveal tract, respiratory mucosal lining, and urinary bladder wall of the pigmented mice. Late-gestation fetuses showed a high accumulation in the eye, inner ear, and respiratory tract. The distribution was similar in the albino mice, except that no accumulation was found in structures corresponding to the melanin-containing tissues of the pigmented mice. The activity levels in the bronchi decreased faster when 2′-^{14}C-nicotine was used. Quantitative measurements of the retention of the two ^{14}C-labeled nicotine preparations confirmed the autoradiographic findings. TLC studies showed that no nicotine was present in the lungs after 24 hr and that only unmetabolized nicotine was present in melanin after 4 hr. Some reactive nicotine metabolites may be responsible for the retention in the urinary bladder wall, which persisted even after rinsing. The accumulation and long-term retention of nicotine in melanin-containing structures might accelerate the development of drug-induced or senile changes in these tissues. An accumulatory mechanism might also participate in the pathogenesis of urinary bladder cancer. (23 refs)

78-6178 **Dietary Fibre and Experimental Colon Cancer (Letter to Editor).** (Eng) Heaton, K. W. (Dept. Medicine, Bristol Royal Infirmary, Bristol BS2 8HW, England); Williamson, R. C. *Lancet* 2(8093): 784-785; 1978.

The protective effect of bran against colon cancer induced by cycasin derivatives in rats, an effect not observed with a diet containing three times the ordinary amount of dietary fiber, may be due at least in part to its lower energy value. Bran-fed animals grew more slowly and, for most of the experiment, their body wt (and thus their carcinogen dose) was only half that of rats receiving the fiber-enriched chow. (11 refs)

78-6179 Protective Effect of Dietary Fibre Against Chemically Induced Bowel Tumours in Rats. (Eng) Fleiszer, D. (McGill Univ. Surgical Clinic and Dept. Pathology, Montreal General Hosp., Quebec, Canada); MacFarlane, J.; Murray, D.; Brown, R. A. *Lancet* 2(8089): 552-553; 1978.

The effects of different levels of dietary fiber (0-28 g/100 g diet) on stool production and on the incidence of dimethylhydrazine-induced (20 mg/kg/wk for 20 wk, sc) large intestinal carcinomas were studied using inbred male Chester Beatty rats. Stool mass and frequency decreased with decreasing dietary fiber, the differences in stool frequency and mass between the highest fiber level group and the other groups being statistically significant ($p < 0.05$). The incidence of colonic carcinoma increased with decreasing fiber content except that the rats given 5 g fiber/100 g diet had more carcinomas (70.6%) than the group given 0 g fiber/100 g diet (42.1%). The difference in carcinoma incidence between the group given the greatest amount of fiber (5.9%) and the other groups was significant. The results support the hypothesis that a diet with high fiber content leads to frequent, bulky stools and a reduced incidence of colonic cancer. (14 refs)

78-6180 Dietary Fibre and Experimental Colon Cancer (Letter to Editor). (Eng) Cruse, J. P. (Surgical Unit, Univ. Coll. Hosp. Medical Sch., London WC1E 6JJ, England); Lewin, M. R.; Clark, C. G. *Lancet* 2(8094): 843-844; 1978.

Several errors in a previous report of a study of the protective effects of dietary fiber against chemically induced rat colon cancer are pointed out. In similar experiments of the authors, dietary fiber did not affect time to tumor or survival of dimethylhydrazine-treated rats significantly. Furthermore, the incidence of colon carcinoma was 100% at 1 yr in all dietary groups, regardless of fiber content. (4 refs)

78-6181 Mutagenic Properties of Ethylidene Gyromitrin and Its Metabolites in Microsomal Activation Tests and in the Host-Mediated Assay. (Eng) von Wright, A. (Food Res. Lab., Technical Res. Center Finland, Biologinkuja 1, SF-02150 Espoo 15, Finland); Niskanen, A.; Pyysalo, H. *Mutat Res* 54(2): 167-173; 1978.

The mutagenicity of the main poisonous hydrazine derivative of the edible mushroom false morel (ethylidene gyromitrin: EG) and its metabolites (N-methyl-N-formylhydrazine and N-methylhydrazine: MFH and MH, respectively) was tested by the microsomal and host-mediated assay. In the microsomal activation tests, the microsomal fraction of mouse liver did not increase the mutagenic or bacteriocidic properties of the EG and its metabolites to *Salmonella typhimurium* strain TA100. None of the compounds caused deaths due to poisoning when given by stomach tube to NMRI mice, although two mice showed typical neurological symptoms after tr ment with EG. EG and MH, but not MFH, inhibited growth of bacteria injected ip into the experimental m There were no increases in mutation frequency in the bact grown in treated mice compared with control bacteria. data confirm the mutagenicity of MH and suggest that s bacteriocidal metabolite is formed from EG. (15 refs)

78-6182 Relationships Between the Mutagenic and C cinogenic Effects of Hydrazine Derivati (Jpn) Shimizu, H. (Dept. Public Health, Jikei Univ. S Medicine, Tokyo, Japan); Hayashi, K.; Takemura, N. *Jp Hyg* 33(3): 474-485; 1978.

The mutagenic and carcinogenic effects of hydrazine der tives were investigated. The microbial mutagenicity of 26 drazine compounds was tested with *Salmonella typhimur* TA98, TA100, TA1537, in the presence or absence of mix. Eighteen of the 26 compounds were known carcinog but the carcinogenicity of the remaining compounds was known. Five carcinogens such as 2-hydroxyethylhydraz butylhydrazine oxalate, phenylhydrazine HCl, beta-phen thylhydrazine sulfate, and p-tolylhydrazine HCl, were mu genic to TA100, with and without the S-9 mix. Two carci gens, hydrazine hydrate and hydrazine sulfate, w mutagenic to TA100 only in the presence of the S-9 m 2,4-Dinitrophenylhydrazine and p,p'-oxybisbenzendis fonylhydrazine, the carcinogenicity of which is unkno were mutagenic to TA100, with and without the S-9 m Phenylhydrazine HCl, p-tolylhydrazine HCl, and 2,4-dinit phenylhydrazine were mutagenic to TA1537, with and wi out the S-9 mix. Phenylhydrazine HCl and p-tolylhydraz HCl were mutagenic to TA98 with the S-9 mix, but 2,4-di trophenylhydrazine was mutagenic to TA98 without the m (78 refs)

78-6183 Transplacental Effect of Urethane on DN Synthesis in Organ Cultures of Murine Emb onic Lung Tissues. (Rus) Kolesnichenko, T. S. (Dept. C cinogenic Agents, Oncological Res. Center, Acad. Medi Sciences USSR, Moscow, USSR); Gusina, N. B. *Biull Ex Biol Med* 86(10): 426-428; 1978.

The effect of transplacental exposure to urethane on DN synthesis in embryonal lung tissue cultures was studied in li A mice. The pregnant mice embryonal lung tissue cultu was studied in line A mice. The pregnant mice received single sc injection of 1 mg/kg urethane on day 15, 17, or of embryogenesis. The embryos were extracted 1 day af injection, cultured, and examined 1, 7, 15, and 21 days lat DNA synthesis was determined from the ^{3}H-thymidine lab ing index. Embryonal lung tissue cultures from untreat pregnant mice served as controls. Urethane inhibited DN synthesis during the first 24 hr; the labeling index was on one-third of that found in the controls. After a normalizatio

e labeling index peaked on day 7 of culture; ie, 8 days after ansplacental exposure to urethane. The labeling index de-eased by day 15 of culture, but it was still higher than that controls. On day 21 of culture, DNA synthesis was seen the experimental explants only, but not in controls. (11 fs)

3-6184 **Effect of Butylated Hydroxytoluene and Paraquat on Urethan Tumorigenesis in Mouse Lung.** Eng) Bojan, F. (Inst. Hygiene and Epidemiology, Univ. edical Sch., 4012 Debrecen, Hungary); Nagy, A.; Herman, . *Bull Environ Contam Toxicol* 20(4): 573-576; 1978.

he effect of administration of butylated hydroxytoluene BHT) or Paraquat on urethan carcinogenesis was studied in e mouse lung. Female CFLP mice (30-35 days old) were eated with BHT (100-800 mg/kg ip) and injected with ure-an (1 mg/g ip) 2 or 26 days before, 2-14 days after, or ncomitantly with BHT. Other mice received a urethan in-ction (1 mg/g ip) concomitantly with or 1-4 days after Para-iat (5, 10, or 20 mg/kg ip). When given alone, BHT and iraquat stimulated mitotic activity in type II alveolar cells id enhanced the carcinogenicity of urethan in the mouse ng. The potentiating effect of BHT was significant when the ethan was given 6-7 days after BHT; the yield of induced ng tumors increased in proportion to the BHT dose. Para-iat also significantly enhanced the number of lung tumors duced by urethan given 2 days after Paraquat; this effect as also dose-dependent. Previous reports have shown that e lung tumors induced by urethan develop from type II veolar cells. These results suggest that BHT and Paraquat hance the carcinogenicity of urethan by increasing the mber of proliferating target cells in the lung. (13 refs)

3-6185 **Vinyl Carbamate as a Promutagen and a More Carcinogenic Analog of Ethyl Carbamate.** (Eng) ahl, G. A. (McArdle Lab. Cancer Res., Univ. Wisconsin enter Health Sciences, Madison, WI, 53706); Miller, J. A.; iller, E. C. *Cancer Res* 38(11, part 1): 3793-3804; 1978.

his study was undertaken to test the hypothesis that vinyl rbamate (VC) is a proximate carcinogenic metabolite of hyl carbamate (EC). When administered topically or ip at e same doses, VC was 10-50 times more active than EC in e initiation of skin tumors and lung adenomas in CD-1 and /Jax mice. VC was mutagenic to *Salmonella typhimurium* A1535 and TA100, but only in the presence of ADPH-fortified rat or mouse liver mitochondrial supernant fractions. This mutagenicity was strongly inhibited by tochrome P-450 inhibitors. EC was not mutagenic for *S. phimurium* in the presence or absence of liver fractions. sts to detect VC as an in vivo metabolite of EC in 5-day-old D-1 and adult A/Jax mice, performed under a variety of nditions, were unsuccessful. However, desaturation of the hyl group during metabolism is suggested by the lower $^{3}H/^{14}C$ ratios in the hepatic DNA, ribosomal RNA, and protein of adult A/Jax mice administered [ethyl-1,2-^{3}H; 1-^{14}C]-EC vs the $^{3}H/^{14}C$ ratios of the EC. The qualitatively similar, but much higher, carcinogenic activity of VC compared to that of EC suggests that the metabolic pathways of these two carbamates may converge in the formation of similar or identical electrophilic reactants that bind covalently to macromolecules in vivo and initiate carcinogenesis. (40 refs)

78-6186 **Tolerances and Exemptions from Tolerances for Pesticide Chemicals in or on Raw Agricultural Commodities.** (Eng) Johnson, E. L. (Office of Pesticide Programs, EPA, 401 M St. SW, Washington, DC, 20460). *Fed Regist* 43(219): 52486-52487; 1978.

An 0.2 ppm tolerance for residues of the herbicide isopropyl *m*-chlorocarbanilate (CIPC) on soybeans has been established. The toxicological data supporting the proposed tolerance included a rat po LD study with an LD of 5-7.5 g/kg, a 2-yr rat feeding study with a no-observable-effect level (NOEL) of 2,000 ppm, a 1-yr dog feeding study with NOEL of 2,000 ppm, two 18-mo mouse carcinogenicity studies at a feeding level of 160 mg/kg/day (negative), a 116-wk mouse carcinogenicity study at a feeding level of 1,000 ppm (negative), a 33-mo hamster carcinogenicity study at a feeding level of 2,000 ppm, and a three-generation rat reproduction study (negative at 1,000 ppm). Desirable data that are lacking are a teratology study, a delayed neurotoxicity study, and an adequate study for effects on cholinesterase. The proposed 0.2 ppm tolerance of soybeans will not contribute residues to the human diet. The 2,000 ppm NOEL in the 2-yr rat feeding study supports an intake of 20 ppm in the human diet using a 100-fold safety factor. A 50 ppm tolerance was previously established for CIPC residues on potatoes, and interim 50 ppm tolerances were established residues on the hay of alfalfa, clover, and grass. (no refs)

78-6187 **Chromosome Investigations of Persons Exposed to Dimethylcarbamoyl Chloride and Diethylcarbamoyl Chloride.** (Eng) Fleig, I. (Occupational Medicine and Health Protection, BASF Aktiengesellschaft, 6700 Ludwigshafen/Rhein, W. Germany); Thiess, A. M. *J Occup Med* 20(11): 745-746; 1978.

Chromosome analyses were made of 10 chemical plant employees who had been exposed to dimethylcarbamoyl chloride (DMCC) and diethylcarbamoyl chloride (DECC) for 4-17 yr and 10 age-matched controls. The frequency of aberrant metaphases in the exposed group was 1.9%, while that in the controls was 1.3%. Chromosome-type aberrations comprised 1.1% of the aberrant metaphases in the exposed subjects and 0.8% in the controls. The differences were not statistically significant, indicating that DMCC and DECC exposure does not cause chromosome damage. (3 refs)

78-6188 **Acetaldehyde Induces Cross-Links in DNA and Causes Sister-Chromatid Exchanges in Human Cells.** (Eng) Ristow, H. (Institut fur Genetik, Freie Universitat Berlin, Arnimalle 5-7, D-1000 Berlin 33, W. Germany); Obe, G. *Mutat Res* 58(1): 115-119; 1978.

Evidence is presented that acetaldehyde (AA), the first metabolite of ethanol, induces cross-links between calf thymus complementary DNA strands and induces sister chromatid exchanges (SCE's) in human lymphocytes. The DNA was incubated for 30 min at 37 C with 1 M AA and dialyzed overnight at 4 C. The DNA was then heated to 90 C, rapidly cooled, and reheated. The thermal transition midpoint (Tm) of AA-treated DNA was 66.2 C during the first heating and 66.6 C during the second. The Tm of control, untreated DNA was 70 C during the first heating, and no characteristic thermal transition was noted during the second. Thus, after heating and cooling, the hyperchromicity of AA-treated DNA was 60% of the original. In contrast, there was only an approx 20% loss of hyperchromicity with control DNA. It is suggested that cross-links were induced between the DNA strands by AA, leading to spontaneous reannealing of part of the DNA after the first heating and resulting in a partial reversal of the hyperchromic effect. Control DNA showed less spontaneous renaturing, possibly because of a lack of cross-links. Hyperchromicity after thermal denaturation was lowered as a function of AA treatment time; spontaneous reannealing after cooling was also related to treatment time. Both processes were dependent on AA concentration. Addition of 0.0005%-0.002% AA 24 or 48 hr before fixation of human lymphocyte cultures induced SCE's in a dose-dependent manner. The number of SCE's produced by the 24-hr treatment was almost doubled when cells were treated for 48 hr. These results indicate that ethanol, via AA, may be mutagenic in humans. (22 refs)

78-6189 **Effect of Colostomy on Intestinal Carcinogenesis of Methylazoxymethanol Acetate in Rats.** (Jpn) Matsubara, N. (First Dept. Surgery, Sch. Medicine, Gifu Univ., Tsukasa-cho, Gifu 500, Japan). *Gifu Daigaku Igakuba Kiyo* 25(6): 501-520; 1977.

The effect of colostomy (COS) on the intestinal carcinogenicity of methylazoxymethanol acetate (MAM acetate) was studied in 5-wk-old Sprague-Dawley rats. Groups 1-3 rats underwent double COS, single COS, and no surgery, respectively, plus treatment with MAM acetate (25 mg/kg/wk x 10, iv). Group 4 rats served as untreated controls. Rats in Groups 1-3 developed multiple intestinal tumors, and the tumor incidence in these groups was similar. Tumor multiplicity was higher in Group 3 than in Group 2. The incidence of colon tumors in Group 1 was 64.5% in the oral one-third of the colon, 83.8% at the COS site, and 41.9% in the anal two-thirds; the mean number of tumors per rat in these locations was 1.4, 1.5, and 0.6, respectively. In Group 2 rats the tumor incidence was 28% in the oral section, 84.0% at the COS site, and 80.0% in the anal section; the mean number of tumors per rat was 0.2, 1.4, and 1.0, respectively. M tumors in the anal section were at the oral stump of the co and they were larger than those in other areas. In Grou tumor incidence was 72.2% in the oral section and 100 the anal section, and the mean number of tumors per rat 1.3 and 4.5, respectively. It was concluded that the carc genic metabolite of MAM acetate can reach the intes mucosa via the vascular system as well as through the bil tract. (24 refs)

78-6190 **Separation and Analysis of Various Carcino ic Aromatic Amines and Their Metabol** (Eng) Weisburger, E. K. (Carcinogen Metabolism and T icology Branch, NCI, Bethesda, MD, 20014); Grantham H.; Benjamin, T. *In: Prevention and Detection of Cancer. ceedings of the Third International Symposium on Detec and Prevention of Cancer Held by the International S Group for the Detection and Prevention of Cancer in York, April 26 - May 1, 1976.* International Study Group the Detection and Prevention of Cancer. (New York, N Vol. 2(Part 1), 2404 pp.; 1961-1972; 1978.

The continued application of various chromatographic tems, including paper, thin-layer, gas, and high-pressure uid chromatography, has led to improvements in the sep tion and identification of metabolites of three carcinog aromatic amines, N-2-fluorenylacetamide, 6-aminochrys and 2,4-toluenediamine. This in turn has increased knowledge of their metabolic pathways. (24 refs)

78-6191 **The Distribution of DNA Repair Synthesis Chromatin and its Rearrangement Follow Damage with N-Acetoxy-2-acetylaminofluorene.** (E Tlsty, T. D. (Dept. Pathology, Washington Univ. Sch. Me cine, St. Louis, MO, 63110); Lieberman, M. W. *Nucleic Ac Res* 5(9): 3261-3273; 1978.

The distribution of DNA repair synthesis in the chroma of confluent human diploid fibroblasts damaged w N-acetoxy-2-acetylaminofluorene (NA-AAF, 5-100 μ was studied. The amount of repair synthesis was depend on NA-AAF concentration up to 10 μM and much less at concentrations >25 μM. Kinetic analysis of staphyloc cal nuclease digestion data showed that more repair synthe occurred in nuclease-sensitive regions of chromatin than nuclease-resistant regions. Data obtained by gel electropho sis were in good agreement with the kinetic data, and th indicated that more repair synthesis occurred in linker DN than in core DNA. Continuous-labeling and pulse-chase periments showed that with time, an increasing proporti of nucleotides inserted during repair synthesis was present the nuclease-resistant regions of chromatin. Rearrangeme involved movement of label incorporated by repair synthe into core DNA. Repair synthesis was a biphasic process. T data suggest that there is a relationship between rates of

synthesis and chromatin rearrangement. (28 refs)

6192 **An Investigation into the Effects of the Carcinogens Benzidine and 2-Acetylaminofluorine AF) on the Control of Cholesterol Metabolism in the Rat the Mouse.** (Eng) Depass, L. R. (Univ. Arkansas Medical ences, Little Rock, AR, 72201). *Diss Abstr Int B* 39(5): 6; 1978. (no refs)

6193 **Enhancement of Rat Hepatocellular-altered Foci by the Liver Tumor Promoter Phenobarbi- Evidence that Foci Are Precursors of Neoplasms and that Promoter Acts on Carcinogen-induced Lesions.** (Eng) tanabe, K. (Kagoshima Univ. Sch. Medicine, 1208-1, ıki-cho, Kagoshima 890, Japan); Williams, G. M. *J Natl ncer Inst* 61(5): 1311-1314; 1978.

e mechanism of liver tumor promotion by phenobarbital 3) was investigated in inbred F344 rats fed 2-fluorenylacetamide (FAA) and an iron-loading diet. ts fed a diet containing 0.02% FAA, 0.8% 8-hydroxuinoline, and 2.19% ferrous gluconate (FG) for 13 wk eloped numerous iron-resistant, altered foci in every sube of the liver. Following cessation of carcinogen feeding, st foci reverted to iron accumulation and could no longer detected by 24 wk, although some persisted for this inter. At the end of 24 wk after FAA termination, 33% and % of two groups of rats had tumors. When 0.05% PB was ded to the diet for 24 wk after termination of FAA, the n-resistant foci persisted, and the incidence of liver lesions s 78%-89%. The same levels of PB in the iron-loading diet rats not given FAA previously did not induce iron-resist- foci. It was concluded that PB did not induce iron-resist- foci, but acted to retard the reversion of FAA-induced i. (33 refs)

-6194 **Diffusion Chamber Cultures for Mutagenic and Carcinogenic Assays (Meeting Abstract).** (Eng) ıang, C. C. (Dept. Experimental Biology, Roswell Park emorial Inst., Buffalo, NY, 14263); Furukawa, M. *Mutat s* 53(2): 201-202; 1978. (no refs)

-6195 **Cyclophosphamide-induced Oncogenic Transformation, Chromosomal Breakage, and Sister romatid Exchange Following Microsomal Activation.** ng) Benedict, W. F. (Div. Hematology-Oncology, Dept. edicine, Childrens Hosp. Los Angeles, Los Angeles, CA, 027); Banerjee, A.; Venkatesan, N. *Cancer Res* 38(9): 22-2924; 1978.

yclophosphamide (CP), an extensively used cancer chemotherapeutic agent, requires metabolic activation through a mixed-function oxygenase system. The capacity of this agent to produce oncogenic transformation and chromosomal damage, including increases in sister chromatid exchanges, was investigated in cultures of C3H/10T1/2CL8 mouse cells and A(T_1) Cl-3 Syrian hamster pseudodiploid cells with or without an exogenous liver metabolic activation system. This system was prepared from the livers of Sprague-Dawley rats inoculated with Aroclor 1254 (500 mg/kg). No oncogenic transformation or chromosomal aberrations were produced by CP in the absence of metabolic activation, whereas significant transformation, chromosomal breaks, and increases in sister chromatid exchanges were observed when the activation system was incorporated into the assays. The oncogenic transformation and chromosomal changes were completely eliminated by removing glucose 6-phosphate and NADP from the system. These studies emphasize the need for incorporating an activation procedure into short-term assays used to evaluate the mutagenic and/or oncogenic potential of various chemicals. (14 refs)

78-6196 **Acute Myelocytic Leukemia 11 Years Following Successful Therapy of Hodgkin's Disease. Report on the Problems of a Second Tumor.** (Ger) Ritter, J. (Kinderklinik der Stadt Braunschweig, Holwedestrasse 16, D-3300 Braunschweig, W. Germany); Oehme, J. *Med Klin* 73(39): 1360-1362; 1978.

Therapy-resistant acute myelogenous leukemia (AML) was diagnosed in a 21-yr-old man who underwent therapy for Hodgkin's disease at the age of 10 and for recurrences at ages 11 and 14-16 yr. The first therapy comprised surgical removal of the tumor, radiation (2,000 rads' focal dose), and several cycles of cytostatics (total doses: 23.6 g cyclophosphamide, 80 mg triethylenemelamine, 40 g procarbazine, 2.3 g chlorambucil, 130 mg vinblastine). Cyclic chemotherapy was repeated with the addition of Ultralan for the recurrences and discontinued 5 yr before the diagnosis of AML. For the first recurrence, radiation (1,600 rads' focal dose) was given. After the diagnosis of AML based on a bone-marrow biopsy, vigorous chemotherapy was given but the patient did not respond. An autopsy showed all the usual signs of AML with no microscopically evident infiltration of Hodgkin's disease. This case suggests that chemotherapy for Hodgkin's disease Stage I or II should not be used without consideration of the possibility of causing a second malignancy. This does not apply to the more advanced stages. A 5% incidence of AML in patients surviving 10 yr after radiotherapy + chemotherapy for Hodgkin's disease has been reported. (13 refs)

78-6197 **Acute Leukemia Following Cyclophosphamide Therapy for Sjogren's Syndrome.** (Eng) Hochberg, M. C. (Rheumatology Div., Good Samaritan Hosp., 5601 Loch Raven Blvd., Baltimore, MD, 21239); Shulman, L. E. *Johns Hopkins Med J* 142(6): 211-214; 1978.

A 56-yr-old woman with Sjogren's syndrome (SS) developed acute myelomonocytic leukemia after 31 mo of cyclophosphamide (CP) therapy (50 mg/day initially, with the dose eventually increased to 150 mg/day). Since the leukemia occurred 12 yr after the onset of SS, CP may have been a significant etiologic factor. (22 refs)

78-6198 **Isolation and Structure Determination of Mutagenic Substances in L-Glutamic Acid Pyrolysate.** (Eng) Yamamoto, T. (Shizuoka Coll. Pharmacy, 2-2-1 Oshika, Shizuoka-shi, Shizuoka 422, Japan); Tsuji, K.; Kosuge, T.; Okamoto, T.; Shudo, K.; Takeda, K.; Iitaka, Y.; Yamaguchi, K.; Seino, Y.; Yahagi, T.; Nagao, M.; Sugimura, T. *Proc Jpn Acad Ser B Phys Biol Sci* 54(5): 248-250; 1978.

Two strongly mutagenic substances produced by pyrolysis of L-glutamic acid were isolated and their structures determined. Pyrolysis was performed by heating 10 kg L-glutamic acid, collecting the resulting tar, distilling the basic fraction, and then purifying this fraction by silica gel, Sephadex column, alumina column, and thin-layer chromatography. Acidification of the two resulting bands with 0.5% HBr produced two hydrobromides with differing Rf values. These compounds were designated Glu-P-1 and Glu-P-20 mutagenicity, determined by the Ames assay, increased with each purification step. The activity of the final purified compounds was 13,700 and 1,600 revertants/μg. Mass spectroscopy and elemental analysis determined that the formulas of Glu-P-1 and Glu-P-2 were $C_{11}H_{10}N_4$ and $C_{10}H_8N_4$, respectively. Nuclear magnetic resonance and UV spectra indicated that the two compounds differed by an aromatic methyl group. The structure of Glu-P-1 was determined to be 2-amino-6-methyldipyrido[1,2-a:3′,2′-d]imidazole, that of Glu-P-2 2-aminodipyrido[1,2-a:3′,2′-d]imidazole. (7 refs)

78-6199 **Azaserine Carcinogenesis: Organ Susceptibility Change in Rats Fed a Diet Devoid of Choline.** (Eng) Shinozuka, H. (Dept. Pathology, Univ. Pittsburgh, Sch. Medicine, Pittsburgh, PA, 15261); Katyal, S. L.; Lombardi, B. *Int J Cancer* 22(1): 36-39; 1978.

The effects of feeding a choline-deficient (CD) diet on the carcinogenicity of azaserine (AS) in the rat pancreas were investigated in groups of male Wistar rats. Groups I and II were fed a CD or choline-supplemented diet, respectively, and inoculated ip with AS (30 mg/kg in 2 ml saline) 2x/wk for the first 4 wk and 1x/wk thereafter, for a total of 14 injections. Control groups were fed either of the diets and inoculated with saline. Four to seven animals from each group were killed 1, 4, and 6 mo after the first injection, and the liver and pancreas were examined histologically. None of the controls developed hepatic or pancreatic tumors, and no hepatomas were observed in the 12 Group II rats. In contrast, 3/5 and 5/7 Group I rats killed at 4 and 6 mo, respectively, had multiple hepatomas. Both Groups I and II rats developed multiple atypical acinar cell nodules (AAC the pancreas after 4 mo. However, the number of AAC significantly smaller in Group I rats (mean, 7.6) th Group II (mean, 16.0). It is concluded that the CD changed the organ susceptibility to the carcinogenic a of AS, enhancing hepatocarcinogenesis and reducing th tion of the carcinogen on the pancreas. (16 refs)

78-6200 **Persistence of DNA Damage in Rat Pan Following Administration of Three Carcin and/or Mutagens.** (Eng) Lilja, H. S. (Dept. Pathology, mouth Medical Sch., Hanover, NH, 03755); Curphey, Yager, J. D.; Longnecker, D. S. *Chem Biol Interact* 22(287-295; 1978.

Alkaline sucrose gradients were used to detect and follo persistence of DNA damage in the pancreas and liver o star and Wistar/Lewis rats after they were given sing multiple weekly injections of azaserine (AZ: 10 mg/kg/ Nδ-(N-methyl-N-nitrosocarbaryl)-L-ornithines (MNC or 218 mg/kg/wk) or neutral red (96 or 288 mg/kg/wk) results were compared with the carcinogenicity mutagenicity of each compound. Damaged DNA was pr in pancreas 1 hr after A2 administration, and damage pe ed in both pancreas and liver for >1 wk. Damage to creatic and hepatic DNA was more extensive 1 wk follo 6 wk or 6 mo of weekly AZ injections than at 1 wk af single injection. Damage to pancreatic DNA was detect rats 1 hr after either dose of MNCO. Pancreatic DNA age was not apparent 1 wk after 72 mg/kg MNCO, but it detectable 1 wk after 218 mg/kg. Significant pancreatic D damage was detected 1 wk after 6 wk or 6 mo of we injections of 72 mg/kg. Damage to hepatic DNA was detectable at either 72 or 218 mg/kg whether administ once or weekly in the above protocols. DNA damage present in pancreas and liver 1 hr after injection of 96 m neutral red but not at 1 wk. Limited DNA damage was tectable in liver but not in pancreas 1 wk after a dose of mg/kg. Persistent DNA damage was also detectable in l but not in pancreas after six weekly injections of 96 mg The results indicate that the relative persistence of D damage may be an accurate indication of the organotr carcinogenic potential of AZ, MNCO and neutral red ad istered at nontoxic dose levels. (17 refs)

78-6201 **On Mutagens in Foods, Especially on C pounds from Pyrolysis of Protein (Meeting** stract). (Eng) Nagao, M. (Natl. Cancer Center Res. I Tokyo, Japan); Yahagi, T.; Kawachi, T.; Seino, Y.; Hon M.; Matsukura, N.; Sugimura, T.; Wakabayashi, K.; Ts K.; Kosuge, T. *Mutat Res* 53(2): 239; 1978. (no refs)

78-6202 **Characteristic Features of Tryptophan Meta lite-induced Hemoblastoses in Various Anim**

cies. (Rus) Khrustalev, S. A. (Cancer Res. Center, Mos-, USSR). *Probl Gematol Pereliv Krovi* 23(9): 33-36; 1978.

e leukemogenic activity of 3-indolylacrylic acid (3-IAA) 2-aminoacetophenone (2-AAP) was studied in Syrian nsters, guinea pigs, and rats. Animals received sc injec- ns of small doses of these tryptophan metabolites for 2-3 . 3-IAA induced hemoblastoses in 10/60 hamsters, 4/71 , and 1/30 guinea pigs; 2-AAP induced hemoblastoses in 5 hamsters, 3/70 rats, and 0/20 guinea pigs (incidence of ntaneous hemoblastoses in hamsters, rats, and guinea pigs 3/33, 2/60 and 1/40 respectively). (4 refs)

6203 **Significance of the Reaction of Nitrite with Tryptophan.** (Eng) Nakai, H. (Natl. Inst. Ani- l Industry, Chiba-Shi, 280, Japan); Cassens, R. G.; Greas- M. L.; Woolford, G. *J Food Sci* 43(6): 1857-1860; 1978.

e reaction of sodium nitrite with tryptophan was studied ctrophotometrically to determine the significance of the ction in cured meats. Although the tryptophan content of at is relatively low, it is an essential amino acid and the ole nitrogen presents a secondary amine for reaction. Ab- ption at 330 nm indicated the formation of nitrosotrypto- n. The reaction proceeded rapidly at pH 4.0, slowly at 5.0 and very sluggishly at pH 5.5 or higher. Experiments h dipeptides and acetyltryptophan indicated that nitrosa- n of the indole nitrogen was promoted if the primary ino group of tryptophan was blocked. It is concluded that, view of the concentration of reactants and pH in cured at, the environment for the nitrosation of tryptophan is r. (18 refs)

6204 **Mutagenic Properties of Nitrosated Spermidine.** (Eng) Kokatnur, M. G. (Dept. Pathology, isiana State Univ. Medical Center, New Orleans, LA, 12); Murray, M. L.; Correa, P. *Proc Soc Exp Biol Med* (1): 85-88; 1978.

e nitrosation of spermidine resulted in direct-acting muta- s in the Ames assay using *Salmonella typhimurium* 1535. The mutagenic effect was catalyzed by thiocyanate inhibited by ascorbic acid. The extent of formation of tagenic compounds was dependent upon the pH of the dium, with an optimum at 4.0 and a range of 3.0-6.0. se results suggest that the nitrosated spermidine model many of the requirements of the hypothesis that gastric cer and its precursor lesions may be induced by the in- gastric formation of mutagenic/carcinogenic N-nitroso npounds. It yields a direct-acting mutagen; it has an op- um pH range very similar to that found in the gastric juice human populations at high risk for gastric cancer, as a ult of chronic atrophic gastritis; its mutagenicity may be anced by thiocyanate ions, which are present in human tric juice, and spermidine is found in foods prominent in diet of populations at high gastric cancer risk. (18 refs)

78-6205 **Effect of L-Ethionine on Macromolecular Synthesis in Mitogen-Stimulated Lymphocytes.** (Eng) Zabos, P. (Dept. Pediatrics and Biochemistry, Mount Sinai Sch. Medicine City Univ. New York, New York, NY); Kyner, D. A.; Seide-Kehoe, R.; Acs, G.; Christman, J. K. *Biochim Biophys Acta* 520(1): 139-152; 1978.

The effects of L-ethionine (Eth) on macromolecular synthesis and modification in mitogen-stimulated human and mouse lymphocytes was studied. DNA synthesis in phytohemagglutinin- or concanavalin A-stimulated lymphocytes was completely inhibited by 2-4 mM Eth. Eth also inhibited the methylation of transfer RNA and prevented the mitogen-induced increase in the activity of histone-modifying enzymes, but it had little or no effect on commitment to DNA synthesis, rates of RNA and protein synthesis, size of the ATP and guanosine triphosphate pools, or the occurrence of morphological changes characteristic of blast formation. Thus, Eth permitted a quiescent lymphocyte to enter the G_1 stage of the cell cycle and to progress toward S, although it blocked DNA synthesis. These effects of Eth were completely reversible: removal of Eth after $\geq$ 24 hr of exposure resulted in the rate of RNA methylation, and an increase in the activity of histone-modifying enzymes. The results suggest that Eth may inhibit DNA synthesis by inhibiting a methylation reaction critical to initiation of that synthesis. (37 refs)

78-6206 **Some Improvements in the Mutagenicity Testing of Chemicals with *Bacillus subtilis, Salmonella typhimurium* and *Escherichia coli*; Results with 500 Chemicals (Meeting Abstract).** (Eng) Hirano, K. (Natl. Inst. Genetics, Misima, Sizuoka-ken, Japan); Narui, K.; Sadaie, Y.; Kada, T. *Mutat Res* 53(2): 200; 1978. (no refs)

78-6207 **Biochemical Studies on Rats with Insulin-secreting Islet Cell tumors Induced by Streptozotocin: With Special Reference to Physiological Response to Oral Glucose Load in the Course of and after Tumor Induction.** (Eng) Kazumi, T. (Second Dept. Internal Medicine, Kobe Univ. Sch. Medicine, Kobe, Japan); Yoshino, G.; Yoshida, Y.; Doi, K.; Yoshida, M.; Kaneko, S.; Baba, S. *Endocrinology* 103(5): 1541-1545; 1978.

Pancreatic islet cell tumors were induced in 32/49 male Wistar rats surviving 9 mo or longer after treatment with streptozotocin (S: 65 mg/kg iv) alone (Group 1), nicotinamide (500 mg/kg ip) + S (Group 2), or picolinamide (250 mg/kg ip) + S (Group 3). Of a total of 73 tumors, there were 14 in Group 1 rats, 47 in Group 2 rats, and 12 in Group 3 rats. In glucose (G) tolerance tests, elevation of blood G following intragastric G was depressed throughout the study in Group 2 rats, and it was significantly depressed at 7 mo. Conversely, mean plasma insulin (I) levels, which had remained unchanged up to 7 mo after treatment, rose abruptly 30 min

after G loading (44 to 167 μU/ml) at 9 mo treatment. In tumor-bearing rats, G levels after loading were always significantly lower than those of tumor-free rats, but mean plasma I levels rose significantly from 47 to 132 μU/ml within 30 min of G administration. Tumor-bearing rats tended to develop hypoglycemia when appearing moribund 13-26 mo after treatment. The mean I concentration in 11 islet cell tumors was 401 U/g wet wt, as opposed to the control mean of 14.0 U/g wet wt. These findings suggest that pancreatic islet cell tumors induced by streptozotocin alone or by combined treatment are insulin-secreting. (8 refs)

78-6208 **Tumorigenic Action of Streptozotocin on the Pancreas and Kidney in Male Wistar Rats.** (Eng) Kazumi, T. (Second Dept. Internal Medicine, Kobe Univ. Sch. Medicine, Kusunoki-cho 7-chome, Ikuta-ku, Kobe 650, Japan); Yoshino, G.; Fujii, S.; Baba, S. *Cancer Res* 38(7): 2144-2147; 1978.

The carcinogenic action of streptozotocin (STZ) was investigated in male Wistar rats. Pancreatic islet cell tumors were induced in 38 of 44 rats which survived 9-14 mo following various treatment schedules with STZ. Single iv injections of STZ alone at doses of 30, 40, 50, and 65 mg/kg produced adenomas of pancreatic islet cells in 8 of 9 (89%), 6 of 7 (86%), 2 of 4 (50%), and 1 of 2 (50%) rats, respectively. The neoplasms were seen in all of 8 rats given a single ip injection of picolinamide (250 mg/kg) 15 min before a single iv injection of STZ (65 mg/kg). Pancreatic islet cell tumors developed in 13 of 14 (95%) rats given a single ip injection of nicotinamide (500 mg/kg) 15 min before a single iv injection of STZ (65 mg/kg). Renal tumors were seen in only 3 rats treated with STZ and nicotinamide. None of the rats used in this study developed hepatic tumors. The results demonstrate that STZ, even in a dose of 30 mg/kg, has an exceedingly marked tumorigenic action on the rat pancreas, while it has little effect on the kidney and no effect on the liver. (19 refs)

78-6209 **Oncogenic Effects of Antimitotic Chemotherapy. Observation of Four Cases.** (Fre) Carcassonne, Y. (Clinique des maladies du sang, Hopital de la Conception, 136, rue Saint-Pierre, F 13385 Marseille Cedex 4, France); Blanc, A. P.; Gastaut, J. A.; Sebahoun, G. *Ann Med Interne (Paris)* 129(3): 181-186; 1978.

Four men developed cancer after undergoing treatment with chemotherapeutic agents. Three patients, ages 24, 53, and 64 yr, had a blood profile and symptoms indicative of acute myeloblastic leukemia after the use of chlorambucil, azathioprine, or 6-mercaptopurine for glomerulonephritis in two cases and immunosuppression prior to kidney transplant in one case. These three patients died of infection or hemorrhage. The fourth patient, age 52 yr, developed a lymphoma after 3 yr of treatment with chlorambucil for glomerulonephritis (total dose, 5,598 g). Combination chemotherapy radiation have succeeded in controlling the malignancy. sible mechanisms of action of the drugs are discussed. refs)

78-6210 **Gastric Cancer in Rats after Chronic traperitoneal Application of Sap of Green P of Potatoes (*Solanum tuberosum* L.).** (Eng) Ivankovi (Inst. Toxicology and Chemotherapy, German Cancer ter, Im Neuenheimer Feld 280, D-69 Heidelberg, W. many). *Experientia* 34(5): 645; 1978.

Sap from the green tops of potatoes (*Solanum tuberosun* was injected ip (0.25 ml) once weekly into 12 BD IX ra determine its carcinogenicity. Two rats developed adeno cinomas of the glandular stomach, and two developed p loma and a squamous cell carcinoma of the forestomach control rats developed tumors. Chemical analysis (un lished) revealed the presence of several volatile N-nit compounds in the sap. (no refs)

78-6211 **Acute Myelogenous Leukemia Following C rambucil Treatment. Report of Two Cases.** (Fiere, D. (Service d'Hematologie, Hopital Edouard Her 5 place d'Arsonval, F 69374 Lyon Cedex 2, France); Feln P.; Vu Van, H.; Coiffier, B. *Nouv Presse Med* 7(9): 756; 1

Two 55-yr-old patients treated with chlorambucil for 2 4 yr for nephrotic syndrome and rheumatoid polyarth respectively, developed acute myelogenous leukemia afte tent periods of 3 and 3.5 yr. (1 ref)

78-6212 **Inhibition of Deoxyribonucleic Acid Synth by Diisopropanolnitrosamine, N-Methylnit ourethane, Azaserine and 4-Hydroxyaminoquinoline-1-o after Partial Pancreatectomy in Rats.** (Eng) Konishi, (Dept. Oncological Pathology, Cancer Center, Nara Med Univ., Kashiwara, 634, Nara, Japan); Denda, A.; Kawab H.; Takahashi, S.; Sunagawa, M.; Kondo, H. *In: Preven and Detection of Cancer. Proceedings of the Third Inte tional Symposium on Detection and Prevention of Cancer by the International Study Group for the Detection and vention of Cancer in New York, April 26 - May 1, 1976.* In national Study Group for the Detection and Preventio Cancer. (New York, NY): Vol. 2(Part 1), 2404 1219-1244; 1978.

The effect of a single injection of dimethylnitrosam (DMH: 100 mg/kg ip), ethionine (700 mg/kg ip), str tozotocin (65 mg/kg iv), diisopropanolnitrosamine (DI 1,000 mg/kg ip), N-methylnitrosourethane (MNUT: mg/kg ip), azaserine (5 mg/kg ip), and 4-hydr yaminoquinoline 1-oxide (4-HAQO: 7 mg/kg iv) on D

hesis of pancreatic acinar cells after partial pancreatecto- (64%) was studied in male Wistar rats. The carcinogens e administered 3 days after the operation, when DNA hesis was at its max level, and the animals were sacrificed later. DNA synthesis was not inhibited by DMN or onine, both nonpancreatic carcinogens. It was inhibited DIPN (57.9%), MNUT (76.4%), azaserine (71.7%), and AQO (82.1%), all pancreatic nonendocrine carcinogens. effect of streptozotocin, a pancreatic endocrine carcino- on DNA synthesis was not clear. Dose-dependent inhibi- of DNA synthesis was seen with azaserine and 4-HAQO not with NMUT or DIPN. The inhibition of DNA syn- is by 4-HAQO lasted for at least 24 hr; it recovered to trol values by 72 hr. Mechanisms involved in the inhibi- of pancreatic DNA synthesis by these carcinogens re- e further study. (36 refs)

6213 **Enzymatic Removal of O^6-Methylguanine from DNA by Mammalian Cell Extracts.** (Eng) Pegg, E. (Dept. Physiology, Milton S. Hershey Medical Center, nsylvania State Univ., Hershey, PA, 17033). *Biochem Bi- ys Res Commun* 84(1): 166-173; 1978.

acts from various rat tissues were incubated with nethylated DNA or chromatin, and their abilities to cata- the removal of labeled O^6-methylguanine (OMG) from -precipitable DNA were compared. The four substrates were dimethylnitrosamine (DMN)-treated DNA and matin, isolated from the livers of rats inoculated with 50 kg ^{3}H-DMN (3.5 Ci/millimole) 20 min before death, and ethyl-N-nitrosourea (NMU)-treated calf thymus DNA NMU-treated rat liver chromatin, obtained by incubat- he two substrates with 0.05 mM ^{3}H-NMU (1.055 Ci/mil- le) in vitro. In the first experiment, the substrates were bated for 60 min at 37 C in the presence or absence of ng liver protein. The rat liver extracts were able to cata- the loss of OMG from acid-precipitable DNA when in- ated with all four substrates. The most convenient sub- te was NMU-treated calf thymus DNA, because it was easiest to prepare and the extracts showed max activity this substrate. Prolonged incubation of the substrate high concentrations of liver protein led to a loss of up 0% OMG. In the second experiment, using extracts from erent rat tissues and NMU-treated calf thymus DNA, liv- xtracts had the greatest activity. Kidney extracts had ut 35% of the liver activity, and extracts from lung, colon, ll intestine, and brain were much less active. The enzyme onsible did not appear to be an N-glycosidase, because abeled OMG could be detected in the supernatant, even igh >50% of this base was lost from the DNA. The ased radioactivity was methanol, which is consistent with possibility that the reaction involves a demethylase action he DNA substrate or on an oligonucleotide derived from 16 refs)

6214 **Further Assessment of a Test for Determining the Mutagenicity of Compounds Metabolised In Vivo in the Rat (Meeting Abstract).** (Eng) Newton, M. F. (Dept. Biology as Applied to Medicine, Middlesex Hosp. Medical Sch., Cleveland St., London W1P 6DB, England); Lilly, L. J. *Mutat Res* 53(2): 241; 1978. (1 ref)

78-6215 **Carcinogen Induced Alterations in DNAase I Release of N^3-Methyladenine from Liver Chromatin.** (Eng) Rao, P. M. (Dept. Pathology, Univ. Toronto, Medical Sciences Building, Toronto, Ontario M5S 1A8, Canada); Rajalakshmi, S.; Sarma, D. S. *Chem Biol Interact* 22(2/3): 347-351; 1978.

To determine whether carcinogens alter gene organization, Fischer rat liver chromatin DNA was labeled in vivo with ^{14}C-dimethylnitrosamine to generate methylated bases such as N^7-methylguanine, O^6-methylguanine, and N^3-methyladenine. The isolated chromatin was treated with pancreatic deoxyribonuclease I (DNase I) to digest 50% of the chromatin DNA, and the distribution of the methylated purines in the DNase I-digestible and nondigestible fractions was determined. Resistance to DNase I was attributed in part to the association of proteins with these regions of DNA. Accordingly, any alteration in the distribution of these dimethylnitrosamine-induced methylated bases in the chromatin fractions as a result of the subsequent administration of carcinogen (N-methyl-N-nitrosourea) was used as a parameter to indicate a change in DNA-protein association in the chromatin brought about by the carcinogen. The observed release of carcinogen-modified bases in the DNase I-digestible fractions of chromatin may represent an interaction of the carcinogen with regions of chromatin that are probably transcribable. The results also indicate that carcinogens can alter the DNA-protein association (gene organization) in such a way that DNA regions in chromatin accessible to nuclease digestion before carcinogen administration are rendered inaccessible subsequent to its administration. (18 refs)

78-6216 **De Novo and Repair Replication of DNA in Liver of Carcinogen-treated Animals.** (Eng) Craddock, V. M. (Toxicology Unit, Medical Res. Council Lab., Woodmansterne Road, Carshalton, Surrey, SM5 4EF, England); Henderson, A. R. *Cancer Res* 38(7): 2135-2143; 1978.

The effect of various carcinogens on de novo and repair replication of DNA in the liver of Wistar rats was investigated. Single ip injections of diethylnitrosamine (100, 200, or 250 mg/kg), ethyl methanesulfonate (300 or 500 mg/kg), aflatoxin (0.5 or 2.0 mg/kg), and retrorsine (160 mg/kg) induced DNA repair replication in vivo but did not alter de novo synthesis 2 hr after injection. Single ip injections of carbon tetrachloride (4,000 mg/kg) and ethionine (500 mg/kg) also induced repair replication but only after a delay period of 17 hr, suggesting that the repair was that of damage caused by an indirect mechanism, such as by deoxyribonuclease activity resulting from lysosomal damage (carbon tetrachloride) or

from nonenzymic reaction of DNA with a metabolite of the carcinogen that is slow to accumulate in the liver (S-adenosylethionine after ethionine). A single ip injection of thioacetamide (150 mg/kg) did not cause detectable repair replication, a result that correlates with the lack of evidence for a reaction between thioacetamide and DNA. (54 refs)

78-6217 **Hepatic Microsomal Metabolism of N,N-Dimethyl-nitrosamine To Its Methylating Intermediate.** (Eng) Chin, A. E. (Univ. Rochester, Rochester, NY, 14627). *Diss Abstr Int B* 39(5): 2243; 1978. (no refs)

78-6218 **Some Peculiarities in the Kinetics and Mechanism of Transformation of Paramagnetic Heme and Non-heme Iron Complexes in Carcinogenesis.** (Eng) Saprin, A. N. (Dept. Kinetics Chemical and Biological Processes, Inst. Chemical Physics, Acad. Sciences USSR, Moscow, USSR). *In: Prevention and Detection of Cancer. Proceedings of the Third International Symposium on Detection and Prevention of Cancer Held by the International Study Group for the Detection and Prevention of Cancer in New York, April 26 - May 1, 1976.* International Study Group for the Detection and Prevention of Cancer. (New York, NY): Vol. 2(Part 1), 2404 pp.; 1207-1218; 1978.

The kinetics of changes in cytochrome P-450 (CCP-450) levels in the Wistar rat liver during dimethylaminoazobenzene (DAB)- and diethylnitrosamine (DENA)-induced carcinogenesis was studied by electron spin resonance. During the precancerous stage, CCP-450 levels in the hyperplastic tissue increased to 2.5 times that of controls and then dropped at the time of tumor appearance and subsequent tumor growth. During the terminal stages of tumor growth, CCP-450 levels decreased fourfold compared with control levels. The free-radical concentration in microsomes increased more than four times during the precancerous stage, compared with normal liver. This increase was observed prior to the decrease in CCP-450 levels, which suggests that the free radicals may be responsible for the decrease. Liver tissue from rats fed both DAB and butylated hydroxytoluene (BHT), a nontoxic inhibitor of free-radical processes, showed no significant change in free-radical concentrations from those in normal tissue, and no tumors developed after 1 yr. However, DAB + BHT increased CCP-450 levels at times earlier than the increase in free-radical concentration. This seems to indicate that the anticarcinogenic properties of BHT are due to its induction of high levels of CCP-450 in rat liver, which promotes the detoxification of DAB, rather than to its inhibition of free-radical formation. (35 refs)

78-6219 **Hematologic Disorder after MOPP Treatment of Hodgkin's Disease.** (Eng) Moloney, W. C. (Massachusetts General Hosp., Boston, MA); Long, J. C.; Ferrucci, J. T.; Groopman, J. E.; Aisenberg, A. C.; Galbadini, J. J.; Dermirjian, Z. N.; Hirsch, M. S.; man, R. M.; Stossel, T. P. *N Engl J Med* 299(17): 946; 1978.

The case report of a man with Hodgkin's disease (HD: n cellularity type) who, 6 yr later at age 35, developed myelogenous or erythromyelocytic leukemia with terr pneumocystis or fungal pneumonia is described. In addi the patient had viral hepatitis, repeated episodes of bact pneumonia, osteomyelitis, cytomegalovirus infection, a hypersensitivity syndrome. After the diagnosis of HD courses of MOPP [nitrogen mustard, vincristine (Onco procarbazine, and prednisone] were administered over 18 The patient improved and was well and active during the 4 yr. Throughout the final illness there was no eviden recurrent HD. The repeated bacterial and viral infection dicated a lack of immunologic defenses. Skin tests for pur protein derivative of tuberculin, streptokinase-strepto nase, and monilia were negative. Whether the splenect after the first diagnosis and the MOPP therapy contrib to the lowering of host defenses is a matter of specula The leukemia may be related to an immunologic d caused by the therapy or to one of many other factors, as injury to lymphoid tissue by the immunosuppressants, haps with activation of a leukemogenic virus. (10 refs)

78-6220 **Dominant Lethal Effects of Triethylenemine in the Guppy *Poecilia reticulata*.** (Mathews, J. G. (Sch. Biology, Georgia Inst. Technology lanta, GA, 30332); Favor, J. B.; Crenshaw, J. W. *Muta* 54(2): 149-157; 1978.

Triethylenemelamine [2,4,6-tris(aziridinyl)-s-triazine, T was selected to test the potential of an experimental d for detecting dominant lethal events in the common gu *Poecilia reticulata*. Dominant lethal effects were induce ip injection of males with 0, 0.1, 0.2, or 0.4 mg/kg T dissolved in Fish Ringer's soln or by immersion of mal the same solns used for the injections for 24 hr. All tr males were subsequently mated to virgin females 1 day treatment, and the females were removed 24 hr later. days following the establishment of matings, the females sacrificed and dissected, and live and dead embryos counted. The percentage of dead embryos increased an total number of embryos decreased with TEM dose. Th jection method had a more deleterious effect than the im sion method, but the reason(s) for this finding are not c The results are compared with those of Drosophila and m malian studies. (17 refs)

78-6221 **DNA Alkylation and Neuro-Oncogenesis 3,3-Dimethyl-l-phenyltriazene.** (Eng) Co H. K. (Max-Planck-Institut fur Hirnforschung, D-5000 K 91, W. Germany); Hauenstein, E.; Kolar, G. F.; Kleihue *Acta Neuropathol (Berl)* 43(1-2): 105-109; 1978.

The role of DNA alkylation in the initiation of malig transformation by 3,3-dimethyl-l-phenyltriazine (DM was studied using BD-IX rats. Following a single sc injec

^{14}C-DMPT (100 mg/kg) into pregnant females on gesta-
n day 21, the concentrations of 7-methylguanine
d O^6-methylguanine in the brains and livers of the
uses were similar. Within 2 days after birth, how-
r, the liver DNA values were significantly higher
n the brain values, and this trend continued during
stnatal growth. In all organs investigated, the con-
ntrations of 7-methylguanine in the DNA of adult
s 12 hr after the last of five weekly injections of
C-DMPT (50 mg/kg each) were higher than those
served 12 hr after a single injection (50 mg/kg).
is effect was most pronounced in the ileum, brain,
d lung. The O^6-methylguanine concentrations follow-
multiple doses of ^{14}C-DMPT were increased only
brain and lung DNA relative to the concentrations
served after a single dose. The data suggest that the
ficient excision repair capacity of the CNS is a signifi-
nt factor in the organ-specific carcinogenicity of
MPT and related carcinogens. (24 refs)

-6222 **Expression of TEM-induced Damage to Post-meiotic Stages of Spermatogenesis of the Mouse uring Early Embryogenesis. II. Cytological Investigations.** ng) Burki, K. (Swiss Inst. Experimental Cancer Res., H-1066 Epalinges, Switzerland); Sheridan, W. *Mutat Res* (1): 107-115; 1978.

nalyses were made of triethylenemelamine (TEM)-induced romosome damage to postmeiotic male germ cells during rly mouse embryogenesis. Male DBA/2J mice treated with 2 or 0.4 mg/kg TEM were mated with CD-1/CR females. or the analysis of first-cleavage metaphases, pregnant nales were treated with 2.5 mg/kg colchicine on day 1 of egnancy, and the eggs flushed from their oviducts approx hr later. In addition, embryos were flushed from the ovi-cts (day 2), junction (day 3), or uteri (day 4) of pregnant nales without colchicine pretreatment. The frequencies of st-cleavage metaphases exhibiting structural aberrations ll of the chromosome type) and the frequencies of two-cell nbryos and of four- to eight-cell embryos containing nuclei companied by micronuclei or nuclei connected by bridges ere closely correlated to frequencies of preimplantation loss embryos recorded in a dominant lethal test. The frequen-es of morulae/blastulae containing blastomeres with mi-onuclei showed a close correlation to the frequencies of tal (pre- and postimplantation) loss of embryos. This indi-tes that the expression of TEM-induced chromosomal mage is delayed and, thus, the damage could persist un-tected in very early stages of embryogenesis. (12 refs)

-6223 **Mutagenicity of Arylalkyl- and Arylacetyl-triazenes in Respect to Their Reaction Mechanisms Meeting Abstract).** (Eng) Pool, B. L. (Inst. Experimental oxicology and Chemotherapy, German Cancer Res. Center, eidelberg, W. Germany). *Mutat Res* 53(2): 249; 1978. (no fs)

78-6224 **Carcinogenicity of Triethanolamine in Mice and Its Mutagenicity after Reaction with Sodium Nitrite in Bacteria.** (Eng) Hoshino, H. (Radiobiology Div., Natl. Cancer Center Res. Inst., Tsukiji, Chuo-ku, Tokyo 104, Japan); Tanooka, H. *Cancer Res* 38(11, part 1): 3918-3921; 1978.

The carcinogenicity of triethanolamine (TEA) was examined in male and female ICR-JCL mice fed a diet containing 0.3% or 0.03% (wt/wt) TEA from the age of 6 wk to death or sacrifice. The incidence of various tumors was significantly higher in TEA-fed mice than in controls. Female mice showed a high incidence of lymphoid tissue tumors (22%), but these tumors were absent in males. Other types of malignant tumors found were independent of sex. Mice fed the TEA-containing diet survived as long as the controls; the survival rate was 50% at 85 wk in females and at 65 wk in males. TEA was not mutagenic to *Bacillus subtilis*, with or without liver microsomes. When TEA was incubated with sodium nitrite under acidic conditions or when the mixture was heated, a direct-acting mutagen was produced, but its mutagenic activity was destroyed by rat liver microsomes. N-Nitrosodiethanolamine (NDEA) was detected in the reaction mixture by thin-layer chromatography, but it may not be the main mutagenic product, because this product was a stable and direct mutagen and its mutagenic activity was destroyed by liver enzymes, whereas NDEA is unstable and does not induce mutation in *B. subtilis* by itself. The chemical nature of the mutagenic product in the TEA:sodium nitrite mixture has not been identified. (11 refs)

78-6225 **Analytical Investigations of Hexamethylenetetramine Samples for the Presence of Volatile Organic Compounds and of In Vitro Nitrosation Metabolites (Nitrosamines).** (Ger) Roper, H. (Institut fur Organische Chemie und Biochemie, Universitat Hamburg, Martin-Luther-King-Platz 6, D-2000 Hamburg 13, W. Germany); Heyns, K. *Z Lebensm Unters Forsch* 167(3): 145-149; 1978.

Analysis of four hexamethylenetetramine (HMT) samples by gas chromatography/mass spectrometry revealed the presence of formaldehyde, methylamine, chloroform, and trimethylamine N-oxide, but no secondary or tertiary aliphatic amines. No dimethylnitrosamine was formed in in vitro nitrosation reactions with HMT + sodium nitrate in acidic soln. In view of these findings, it is proposed that HMT be reconsidered for use as a food additive. (36 refs)

78-6226 **Combined Action of Alkylating Compounds on Human Chromosomes (Meeting Abstract).** (Eng) Bochkov, N. P. (Inst. Medical Genetics, USSR Acad. Medical Science, Moscow, USSR); Yakovenko, K. N.; Nazarenko, S. A. *Mutat Res* 53(2): 152-153; 1978. (no refs.)

78-6227 **Metabolic Activation of Nitrofurans by Testis Homogenate from Mammals (Meeting Abstract).** (Eng) Maier, P. (Environmental Mutagenesis Branch, Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC); Chhabra, R. S. *Mutat Res* 53(2): 226; 1978. (1 ref)

78-6228 **Direct Study of Alkylating Agent-RNA Interaction by ^{13}C Nuclear Magnetic Resonance Spectroscopy.** (Eng) Chang, C. (Dept. Medicinal Chemistry and Pharmacognosy, Sch. Pharmacy and Pharmacal Sciences, Purdue Univ., W. Lafayette, IN, 47907); Lee, C. G. *Cancer Res* 38(11, part 1): 3734-3736; 1978.

The interactions of four methylating agents and *Torula* yeast RNA were studied by ^{13}C nuclear magnetic resonance (NMR) spectroscopy, a direct method that eliminates all processes that may cause decomposition and structural alteration. In addition, spectral interference is reduced, product distribution can be determined at an early alkylation stage, and the amount of alkylating agent can be reduced. Methylation reactions were carried out at room temperature and pH 7 by treating an 8.5-ml aqueous soln of 500 mg lyophilized RNA with 1.5 millimoles of methyl methanesulfonate (MMS: 130 μl), dimethyl sulfate (DMS: 142 μl), or 1-methyl-1-nitrosourea (MNNG: 221 mg) for 12 hr or with 1-methyl-3-nitro-1-nitrosoguanidine (MNNG: 221 mg) for 259 hr. Each reaction mixture was then dialyzed and lyophilized repeatedly, and NMR samples were prepared. Based on integration curves, the agents could be classified into two groups according to biological potency: (1) weakly mutagenic/carcinogenic, MMS and DMS; (2) strongly mutagenic/-carcinogenic, MNU and MNNG. In conclusion, from the chemical shift analyses and the spectral integration curves, the reactive sites, the product distributions and specificity of the different methylating agents, and the degree of N-7 methylation of guanosine could be determined. The results show the potential application of ^{13}C NMR spectroscopy in establishing the mechanisms of chemical carcinogenesis and mutagenesis. (32 refs)

78-6229 **N-Methyl-N-nitrosourea Mediated Conversion of O^6-Methylguanine to Xanthine.** (Eng) Rao, P. M. (Dept. Pathology, Univ. Toronto, Medical Sciences Building, Toronto, Ontario M5S 1A8, Canada); Rajalakshmi, S.; Serma, D. S.; Krepinsky, J. *Chem Biol Interact* 22(2/3): 341-346; 1978.

The in vitro alkylation by N-methyl-N-nitrosourea (MNU) of rat liver chromatin DNA prelabeled in vivo with ^{14}C-dimethylnitrosamine (^{14}C-DMN) was studied. The standard reaction condition was to incubate 4.24 micromoles (μmol) of (^{14}C) methylguanine [O^6-(^{14}C)meG] in 0.1 N HCl at 70 C 45 min or at 37 C for 16 hr. In all cases, demethylation O^6-meG yielded guanine. However, when treated with MI (29.1 μmol) and 0.1 N HCl, O^6meG was converted mo to xanthine. Observations that guanine is not deaminated MNU and 0.1 N HCl as effectively as O^6-meG and that guanine is detected in the formation of xanthine from meG suggest that the deamination of O^6-meG precedes demethylation step in its conversion to xanthine. It is suggested that if the conversion of O^6-meG to xanthine occ in vivo at the macromolecular level, the mutagenicity N-nitroso-N-alkylamides can be due to not only the for tion of a miscoding lesion of O^6-meG, but also to its conv sion to xanthine. (9 refs)

78-6230 **C-Type Virus Particles in Cell Cultures o Chemically Induced Glioma in Sprague-Daw Rats.** (Rus) Anzil, A. P. (Electron Microscopy Lab., M Planck Inst. Psychiatry, Munich, W. Germany); Stavrou, Blinzinger, K. *Vopr Onkol* 24(9): 30-32; 1978.

Long-term cultures were prepared from mixed anaplastic omas induced by N-methyl-N-nitrosourea (6 mg/kg/wk for at least 10-12 mo) in Sprague-Dawley rats. Electron croscopy revealed budding and large numbers of cytoplas and extracellular C-type virus particles in many cultu This is the first report of a chemically induced glioma sociated with C-type virus particles in rats. The characte tics of this rat glioma are being studied. (10 refs)

78-6231 **Surface Structure of Fetal Rat Brain Cells D ing Neoplastic Transformation in Cell Cultu** (Eng) Haugen, A. (Dept. Pathology, Gade Inst., Univ. B gen, N-5016 Haukeland Hosp., Bergen, Norway); Laeru O. D. *J Natl Cancer Inst* 61(6): 1415-1422; 1978.

The surface microstructure of fetal BD IX rat brain c undergoing neoplastic transformation in long-term cell c ture after they were exposed to a single transplacental pu of N-ethyl-N-nitrosourea (ENU; 75 μg/g) on gestation d 18 was investigated by scanning electron microscopy. T fetal brain cells (FBC) were transferred into monolayer c ture 24 hr after exposure and maintained in culture for to 1.5 yr. After 3 wk, ENU-pretreated FBC showed fo proliferation of neural cells on an underlayer of flat, epithe oid cells. The neutral cells exhibited varying forms of num ous dorsal ruffles and an increased number of other surfa microprojections. Between the 40th and 100th day, nodu of bipolar and multipolar neutral cells with a complex surfa microstructure, including many blebs and ruffles and an creased number of microvilli, were observed. After 100 da more rapidly proliferating, morphologically altered ce

ned piled-up foci, which resulted in a homogeneous popu-
on of cells with numerous long microvilli, large ruffles,
blebs over the whole surface. Attempts to establish per-
ent cell lines were successful in 4/13 trials. Three of these
lines were tumorigenic upon retransplantation into baby
at around 273 days. The surface structure of cells from
solid tumors was the same as that seen in vitro, exhibiting
nerous microvilli and ruffling membranes over the whole
face. Thus, surface alterations characteristic of neoplastic
s were observable > 100 days before the cells became
norigenic. (29 refs)

6232 **Mutagenicity of Several Classes of Antitumor Agents to *Salmonella typhimurium* TA98, 100, and TA92.** (Eng) Seino, Y. (Biochemistry Div., Natl. ncer Center Res. Inst., Tsukiji, Chuo-ku, Tokyo 104, Ja-); Nagao, M.; Yahagi, T.; Hoshi, A.; Kawachi, T.; imura, T. *Cancer Res* 38(7): 2148-2156; 1978.

e mutagenic activities of various antitumor agents which uded 19 antimetabolites, 5 antibiotics, 5 alkylating agents, kaloids, 1 enzyme, and 1 adrenal steroid hormone were ed on *Salmonella typhimurium* strains TA100, TA98, and 92. Four of the anticancer agents, busulfan, carbazilqui-e, 1-(4-amino-2-methylpyrimidine-5-yl)methyl-3-(2-chlo-thyl)-3-nitrosourea hydrochloride, and pipobroman were wn to be mutagenic for the first time. The known muta-icities of five others, daunomycin hydrochloride, mitomy-C, 6-mercaptopurine, and cyclophosphamide were con-ned. Since there is a demonstrated correlation between tagenicity in this bacterial test system and the carcinogen-otential in laboratory animals, the development of new motherapeutic agents that have no mutagenicity in such terial test systems is desirable from the standpoint of pos-y decreasing the risk of latent drug-induced cancer in pa-nts undergoing chemotherapy. (33 refs)

6233 **Alloxan Induced Leukemoid Condition in a Fresh Water Teleost *Clarias batrachus* (Letter Editor).** (Eng) Agrawal, P. (Dept. Zoology, M.M./P.G. ll., Modinagar 201 204, District Ghaziabad, Uttar Pra-h, India); Goel, K. A. *Curr Sci (Bangalore)* 47(15): -560; 1978.

ossible leukemogenic action of alloxan was demonstrated 42 fish (*Clarias batrachus*) inoculated im with 50 mg/kg the compound every 3 days. The number of WBC in-ased after 10-40 days, and after 40 days, 50% of the total BC were immature. Mitosis was also observed in some BC at this time. (2 refs)

6234 **Mutagenicity of Nitro Compounds in *Drosophila melanogaster* (Meeting Abstract).** (Eng) Kramers, P. G. (Dept. Radiation Genetics and Chemical Mutagenesis, State Univ. Leiden, Wassenaarseweg 72, Leiden, Netherlands). *Mutat Res* 53(2): 213; 1978. (no refs)

78-6235 **Flagyl and Radiation-induced Chromosome Breakage (Letter to Editor).** (Eng) Prosser, J. S. (Natl. Radiological Protection Board, Harwell, Didcot, Oxon OOX11 0RQ, England); White, C. M. *Br J Radiol* 51(608): 654-655; 1978.

Preliminary observations of the effect of Flagyl (metronidazole) on the yield of x-ray-induced dicentric aberrations in human lymphocytes from anoxic and normal venous blood are presented. Flagyl increased the dicentric yield from irradiated anoxic blood significantly, but the dicentric levels were not as high as those observed in normal venous blood. The dicentric yield from blood at venous oxygen tension was not changed. (7 refs)

78-6236 **The Mutagenic Screening of Fourteen Imidazo Compounds Using a Modified Ames' Test.** (Eng) Turner, J. V. (Dept. Tissue Pathology, Inst. Medical and Veterinary Science, P.O. Box 14, Rundle St., Adelaide, S. Australia, 5000, Australia); Ward, A. D.; Freeman, C. G. *Mutat Res* 57(2): 135-139; 1978.

Eight imidazo[1,2-a]pyrimidine derivatives and six cyclic guanidine derivatives were synthesized and tested for mutagenic activity by a modified Ames *Salmonella typhimurium* assay using strains TA100, TA98, and TA1537, with or without microsomal activation. No mutagenicity or inhibition of growth was observed with any test compound. (6 refs)

78-6237 **High Pressure Liquid Chromatographic Assay for α Hydroxylation of N-Nitrosopyrrolidine by Isolated Rat Liver Microsomes.** (Eng) Chen, C. B. (Div. Environmental Carcinogenesis, Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY, 10595); McCoy, G. D.; Hecht, S. S.; Hoffmann, D.; Wynder, E. L. *Cancer Res* 38(11, part 1): 3812-3816; 1978.

A high-pressure liquid chromatographic assay for the α hydroxylation of N-nitrosopyrrolidine (NPY) by isolated hepatic microsomes from Aroclor-induced or noninduced male F-344 rats is described. This sensitive assay may allow determination of the role of hydroxylation in NPY carcinogenesis. Mixtures consisting of NPY, rat liver microsomes, and an NADPH-generating system were incubated at 37 C. The major α hydroxylation product, 2-hydroxytetrahydrofuran, was trapped by the addition of 2,4-dinitrophenylhydrazine to form 4-hydroxybutyraldehyde-2,4-dinitrophenylhydrazone, which was then quantitated by reverse-phase high-pressure liquid chromatography. Under optimal conditions, the α hy-

droxylation of NPY was linear for at least 90 min and had characteristics typical of the microsomal mixed-function oxidase system, such as inhibition by carbon monoxide and induction by pretreatment of the rats with Aroclor (500 mg/kg). Aroclor induction resulted in a greater than twofold increase in the α hydroxylation rate compared with noninduction. There was a close correspondence between the binding affinity and the α hydroxylation of NPY by the microsomes. This is the first available method for in vitro studies of the α hydroxylation of a cyclic nitrosamine. (28 refs)

78-6238 **The Effect of the Microsomal Enzyme Inhibitor, Piperonyl Butoxide, on Mutagenesis in *Drosophila melanogaster* (Meeting Abstract).** (Eng) Lindsay, R. J. (Sch. Biological Sciences, Flinders Univ. South Australia, Bedford Park, S.A. 5042 Australia); Clark, A. M. *Mutat Res* 53(2): 221; 1978. (no refs)

78-6239 **Structural Requirements for Mutagenic Activities of N-Heterocyclic Bases in the Salmonella Test System.** (Eng) Matsumoto, T. (Central Res. Inst., Japan Tobacco and Salt Public Corp., 6-2, Umegaoka, Midoriku, Yokohama, Kanagawa 227, Japan); Yoshida, D.; Mizusaki, S.; Tomita, H.; Koshimizu, K. *Agric Biol Chem* 42(4): 861-864; 1978.

The effects of structural changes on the mutagenic activities of quinoline (Q), isoquinoline (IQ), phenanthridine (PA), benzo(f)quinoline [B(f)Q], benzo(h)quinoline [B(h)Q], and their α-amino derivatives were studied in the *Salmonella typhimurium* test system. All mutagenic compounds tested required the liver microsomal fraction (S-9 mix) in order to express their mutagenic activity. PA, B(f)Q, and Q were mutagenic to strains TA98 and TA100, B(h)Q was mutagenic only to TA100, and IQ was nonmutagenic to both strains. The mutagenic activities of Q and the BQ's increased greatly after amination in the α-position of the pyridine moiety, but amino-IQ was nonmutagenic to TA98 and TA100. The addition of a benzene ring to 2-amino-Q markedly increased its mutagenic activity, whereas the addition of a benzene ring to the pyridine moiety of 2-amino-Q only slightly increased mutagenic activity. The mutagenic activity of 2-amino-B(f)Q, but not those of 2-amino-B(h)Q and 9-amino-PA, was markedly stimulated by B(f)Q, B(h)Q, and PA in the presence of S-9 mix. Norharman enhanced the effect of 2-amino-B(f)Q in the presence of S-9 mix. The results indicate that among the α-amino heterocyclic bases, a three-ring system is more mutagenic than a two-ring system and the fused position of the three-ring system affects mutagenic activity and strain specificity. (15 refs)

78-6240 **Carcinogenicity of 4-Chloronitrosopiperidine in Sprague-Dawley Rats.** (Eng) Lijinsky, W. (Chemical Carcinogenesis Program, NCI Frederick Can Res. Center, Frederick, MD, 21501); Taylor, H. W. *Z Kr forsch* 92(2): 217-220; 1978.

The carcinogenicity of 4-chloronitrosopiperidine was tes in 15 Sprague-Dawley rats who were given the compoun their drinking water (0.005% soln) for 27 wk (total dose, mg). Seven animals died by 41 wk, all 15 by 58 wk. Twe rats had tumors: 7 had liver tumors, 5 had esophageal mors, 2 tumors of the nonglandular stomach, and 2 tum of the nasal turbinates. Several rats had tumors of more th one organ. The mortality pattern of these rats was alm identical with that of rats treated with a considerably hig dose (440 mg) of nitrosopiperidine. It is concluded that addition of a single chlorine atom to the nitrosopiperid molecule changes the chemistry so that the compound more active in producing liver neoplasms. (5 refs)

78-6241 **Formation and Biological Effect of N-Nitr Compound from Piperazine Pesticide Trifori** (Eng) Borzsonyi, M. (Dept. Morphology, Natl. Inst. Pub Health, Budapest, Hungary); Pinter, A.; Torok, G.; Surj A.; Nadasdi, L. *IARC Sci Publ* (19): 477-484; 1978.

In vitro experiments were conducted to determine the form tion of the carcinogen dinitrosopiperazine (DNPZ) from t fungicide Triforine (TF: N,N'-piperazinidylbis-2,2,2-t chloroethylidenebisformamide), and in vivo experime were conducted in Swiss/Leiden mice to determine tum incidence and morphology after intragastric administrati of TF (300 mg/kg 2 x/wk). One hundred of the mice a received 0.05% sodium nitrite in their drinking water (Gro 1), and 50 were treated with TF alone (Group 2). Tum incidence was highest in Group 1 (104 tumors), and most the tumors were lymphomas. The proliferating tumor ce corresponded to lymphoblasts. Ten Group 1 mice had sto ach tumors, four gastric papillomas and six invasive squ mous cell carcinomas. Prior to day 180, however, there we no morphological alterations in the glandular mucosa of t stomach. Most of the intestinal tumors that developed we in the duodenum and jejunum, and tumors appeared to dev op from surface foci of atypical epithelial cells. Tumor in dence was similar in Group 2 animals, animals treated wi sodium nitrite only, and untreated controls, and it was muc less than that of Group 1 (25 tumors/401 mice). The resul indicate that various tumors can be induced by DNP formed in vivo from TF. In the in vitro nitrosation of T 100 g of TF was dissolved in 270 ml 6 N HCl and 47.6 of sodium nitrite dissolved in 270 ml distilled water was a ded slowly. After 24 hr at 4 C, 15.8 g of 1,4-dinitropiperazi was formed. (8 refs)

78-6242 **Chemical Carcinogen Alteration of SV40 Vir Induced Transformation of Normal Human Ce Populations In Vitro.** (Eng) Milo, G. E. (Dept. Physiologic

emistry, Coll. Medicine, Ohio State Univ., 1900 Coffey d, Columbus, OH, 43210); Blakeslee, J. R.; Hart, R.; an, D. S. *Chem Biol Interact* 22(2/3): 185-197; 1978.

in vitro interactions of chemical carcinogens with a sforming DNA virus in human cells were determined to n index of the cocarcinogenicity of these agents. The fre- ncy of simian papovavirus 40 (SV40)-induced transforma- of human foreskin fibroblasts or neonatal foreskin cells enhanced after pretreatment of the cells with naphthyla- e-2 (NA-2), N-methyl-N′-nitrosoguanidine (MNNG), cetyl-2-fluorenylacetamide (N-Ac-AAF), benzo(a)py- e (BP), aflatoxin B_1 (AFB_1), propane sultone, β-propiolac- e (βPL), 4-nitroquinoline oxide (4-NQO), methylme- ne sulfonate (MMS), or diethylnitrosamine (DEN). ttreatment with 4-NQO, MMS, MNNG, or DEN inhibit- transformation, but posttreatment with AFB_1, β-PL, or -2 did not alter transformation, similar to the action of Ac-AAP and BP. All carcinogens that altered transforma- after pretreatment damaged cellular DNA. Pretreatment posttreatment with 3-methylcholanthrene (3-MC) or 2-dimethylbenz(a)anthracene (7,12-DMBA) did not dam- cellular DNA and did not enhance transformation. More- r, pre- or posttreatment with other weak or noncarcino- s that did not damage cellular DNA also did not alter is-induced transformation. All foci formed in the cocar- ogen-treated cultures, whether the carcinogen inhibited or anced transformation, were virus-directed. Although a ilar pattern of response existed for carcinogens that either ance or inhibit transformation, each of the carcinogens t enhanced or inhibited foci formation damaged cellular IA. Moreover, those carcinogens that enhanced focus for- tion, compared with the carcinogens that inhibited focus nation, exhibited similar DNA damage profiles. (35 refs)

6243 **Breast Cancer at a Psychiatric Hospital Before and after the Introduction of Neuroleptic ents.** (Eng) Wagner, S. (Office Medical Director, Norris- n State Hosp., Norristown, PA, 19401); Mantel, N. *Can- Res* 38(9): 2703-2708; 1978.

e possible association between breast cancer and treatment h neuroleptic agents was investigated in 5,463 women who d or underwent breast biopsy at the Norristown State Hos- al (in Pennsylvania) between 1940 and 1974. The method oroportionality was used to evaluate the breast cancer inci- ace. Cases of breast cancer were related to deaths from er cancers and to deaths from all causes other than breast cer. Deaths and cancers that occurred within 1 yr of hos- al admission were excluded from the analysis. To allow for 0-yr transition period and for latency in the development breast cancer, comparison was made between the 15 yr ceding the introduction of neuroleptic agents into medical ctice (1940-1954) and the second decade after their intro- ction (1965-1974). Although neuroleptic agents were used ensively to treat the patients at the hospital, there was no tistically or medically significant change in the indicated incidence of breast cancer at the hospital during the neuroleptic period. The study did not rule out the possibility that neuroleptic agents might have some effect on breast cancer after a very long latency period. (no refs)

78-6244 **Investigation on the Tester Strain of *Saccharomyces cerevisiae* for Primary Screening of Environmental Mutagens (Meeting Abstract).** (Eng) (Div. Genetics, Natl. Inst. Radiological Sciences, Chiba, Japan); Machida, I.; Saeki, T.; Yoshikawa, K. *Mutat Res* 53(2): 240; 1978. (no refs)

78-6245 **Neoplastic Transformation of Human Diploid Cells In Vitro after Chemical Carcinogen Treatment.** (Eng) Milo, G. E. (Dept. Physiological Chemistry and Veterinary Pathobiology, Ohio State Univ., 1900 Coffey Road, Columbus, OH, 43210); DiPaolo, J. A. *Nature* 275(5676): 130-132; 1978.

The in vitro neoplastic transformation of primary or low-passage cells from 10 human foreskin cell populations by the carcinogens propane sultone (PS: 5 μg/ml), β-propiolactone (PL:13 μg/ml), aflatoxin B_1 (AFB_1: 10 μg/ml), N-methyl-N′-nitro-N-nitrosoguanidine (MNNG: 0.1 μg/ml), 4-nitroquinoline 1-oxide (4-NQO: 0.002 μg/ml), and ethyl methane sulfonate (EMS: 10.0 μg/ml) is reported. To obtain transformation, the normal cells were blocked in the G_1/S interphase, released, and then treated with carcinogen during the S phase. Removal of the carcinogen 12 hr later coincided with the end of the S phase. After treatment, the proliferation of the unaffected cell population was purposely inhibited. Posttreatment population doubling No. 20 was found to be suitable for determining the ability of the transformed cells to grow in 0.5% soft agar. Cells transformed by PS, PL, and AFB_1 had 100% colony-forming ability in soft agar, whereas only 25%-70% of those transformed by 4-NQO, EMS, and MNNG formed colonies. A close correlation between growth in soft agar and tumor formation in nude mice was obtained. Injection of cells into the subcapsular area of the mice produced sc tumors 18-25 days later. The tumors were composed of multiple vacuolated cell types having predominantly a syncytial network with an eosinophilic cytoplasm and ovoid basophilic nuclei. The tumors were classified as undifferentiated mesenchymal tumors. To date, tumors have been serially subpassaged three times. (15 refs)

78-6246 **Rat Liver Microsome-Mediated Binding to DNA of 3-Amino-1-methyl-5*H*-pyrido[4,3-*b*]indole, a Potent Mutagen Isolated from Tryptophan Pyrolysate.** (Eng) Hashimoto, Y. (Faculty Pharmaceutical Sciences, Univ. Tokyo, Bunkyo-ku, Tokyo, Japan); Takeda, K.; Shudo, K.; Okamoto, T.; Sugimura, T.; Kosuge, T. *Chem Biol Interact* 23(1): 137-140; 1978.

The binding of 3-amino-1-methyl-5H-pyrido(4,3-b)indole (Trp-P-2) to calf thymus DNA was measured after incubation with liver microsomes from male Wistar rats treated with polychlorinated biphenyl (500 mg/kg, ip). The radioactivity from ^{3}H-Trp-P-2 bound tightly to DNA in the presence of rat liver microsomes. The binding was not affected by reprecipitation, dialysis, or gel chromatography. The amount of Trp-P-2 bound to DNA was about 60 μmol/mol P, which increased to 230 μmoles/mole P after three successive incubations of the DNA with Trp-P-2- and microsomes. Trp-P-2 bound significantly to poly G in the presence of microsomes, but it did not bind to poly A, poly C, or poly U in the presence or absence of microsomes. After acid hydrolysis, DNA with bound Trp-P-2 gave more than two fluorescent spots on thin layer chromatography. (8 refs)

78-6247 **Guanyl O^{6}-Arylamination and O^{6}-Arylation of DNA by the Carcinogen N-Hydroxy-1-naphthylamine.** (Eng) Kadlubar, F. F. (Natl. Center Toxicological Res., Jefferson, AR, 72079); Miller, J. A.; Miller, E. C. *Cancer Res* 38(11, part 1): 3628-3638; 1978.

Two O^{6}-substituted deoxyguanosine adducts formed by the reaction of N-hydroxy-1-naphthylamine (N-HO-1-NA), a carcinogen for liver, urinary bladder, and other tissues of humans and animals, with DNA at pH 5 were isolated and characterized. N-HO-1-NA reacted with nucleic acids and protein at pH 5 to form covalently bound derivatives with 3-20 naphthyl residues/1,000 monomer units. The level of binding was in the following order: DNA > polyguanylic acid > denatured DNA and ribosomal RNA > serum albumin > transfer RNA > polyadenylic acid. The carcinogen did not react with nucleosides and nucleotides. Binding of N-HO-1-NA to DNA was not inhibited by the addition of nucleosides, nucleotides, methionine, or glutathione. Enzymatic hydrolysis of the DNA-containing naphthyl residues yielded three nucleoside arylamine adducts, N-(deoxyguanosin-O^{6}-yl)-1-naphthylamine, 2-(deoxyguanosin-O^{6}-yl)-1-naphthylamine, and the decomposition product of the latter. Direct evidence for acid-dependent arylnitrenium ion formation was obtained by isotope exchange upon solvolysis of N-HO-1-NA in acidic $H_2{}^{18}O$, and carbocation formation was indicated by formation of the solvolysis products 1-amino-2-naphthol and 1-amino-4-naphthol. The potential role of the guan-O^{6}-yl naphthylamine adducts in the initiation of urinary bladder carcinogenesis through the formation of promutagenic lesions in DNA is discussed. (64 refs)

78-6248 **Follicular and Parafollicular Adenomas in the Thyroids of Rats Treated with Thiamazole.** (Fre) Stoll, R. (Laboratoire de la Fondation Bergonie, 180 rue de St. Genes, F 33076 Bordeaux Cedex, France); Faucounau, N.; Maraud, R. *Ann Endocrinol (Paris)* 39(3): 179-189; 1978.

The development of follicular cell (FC) and parafollicular (PFC) adenomas in the thyroids of rats treated with the thyroid drug thiamazole (TMZ: 1-methyl-2-mer toimidazole) was followed. Three groups of male Wistar ages 3, 6, and 8 mo respectively, were administered 0.1% 0.2% TMZ in their drinking water for 1, 3, 8, 9, 12, o mo. The rats were killed and their thyroids examined mediately after the end of treatment or at various time to 17 mo later. Control rats of same age were also sacrifi Immediately after treatment, animals on TMZ for 1-3 mo thyroid glands that were larger and heavier than cont hypertrophy and hyperplasia were evident, but no adeno were observed. Rats sacrificed immediately after 8 m treatment had one or more FC adenomas, some of w occupied an entire lobe of the thyroid. PFC adenomas d loped in rats starting 6 mo after the cessation of TMZ t ment. In rats treated for 3 mo, the PFC adenomas were only type observed after cessation of treatment; in rats tre for 8 mo or more, PFC adenomas coexisted with FC ad mas. Among the 72 rats treated for 9-14 mo, 64 had ad mas, 46 FC, 7 PFC, and 11 FC + PFC types. The percen of C cells (or parafollicular cells, of which the PFC adeno are composed) increased with age of rat. C-cell hyperpl occurred in rats during TMZ treatment, but no PFC ad mas were formed until treatment had stopped. It is conclu that both types of adenomas are related to the hypothy condition and its duration, but the hormonal mechanism volved differs. (19 refs)

78-6249 **3-Hydroxyxanthine: Transplacental Effect Ontogeny of Related Sulfate Metabolism Rats and Mice.** (Eng) Anderson, L. M. (Memo Sloan-Kettering Cancer Center, Walker Lab., Rye, N 10580); McDonald, J. J.; Budinger, J. M.; Mountain, I. Brown, G. B. *J Natl Cancer Inst* 61(6): 1405-1410; 197

Sulfotransferase activity toward the carcinogenic pu N-oxide 3-hydroxyxanthine (3-OH-X) was detected in f Sprague-Dawley (SD) rats and (C57BL/6 x BALB/c)F$_1$ m delivered near term at a rate of approx 25% of a values. The activities of 3-OH-X sulfotransferase, ^{3} 3′-phosphoadenosine-5′-phosphosulfate (PAPS) su hydrolase and ^{35}S-p-nitrophenol (PNP) sulfotransfe were compared in an assay using homogenized livers. At day 21 of gestation, 3-OH-X sulfotransfe activity in fetal livers was significantly lower t adult values, and treatment of pregnant females w 3-OH-X (25 mg/day 4x) did not alter the enzyme levels. A er birth, the activity rose linearly to adult values at 6 wk. P sulfotransferase was low or absent in fetal livers, but af birth, it eventually reached adult levels at 6 wk. PAPS s fohydrolase was 2-3 times higher in fetal livers than in liv of pregnant females or 6-wk-old rats, and it fell steadily adult values after birth. 3-OH-X was injected ip into pregn rats four times at doses of 1, 5, 10, or 25 mg on days 19- of gestation; pregnant mice were injected ip with 50 mg/ on days 17 and 18. Of 10 male rat offspring receiving 25 m doses prenatally, 3 had liver tumors (including 2 hepatoma

npared with 0/29 controls. Kidney disease at all doses was nmon in male rats, but no liver abnormalities were seen female offspring. Prenatal administration of 3-OH-X in e significantly increased prenatal deaths, but the survivors l fewer lung adenomas at 20 mo of age (6/28 vs 21/50 trols). The association of low levels of activating enzyme male fetal rat liver with the weak but significant tumori- ic effect of 3-OH-X supports the hypothesis that enzymat- ctivation may be a limiting factor in transplacental car- ogenesis. (25 refs)

-6250 **Increased Incidence of Mammary Tumors in Rats After Direct or Transplacental Exposure 3-Hydroxyxanthine.** (Eng) Anderson, L. M. (Memorial an-Kettering Cancer Center, Walker Lab., Rye, NY, 580); Teller, M. N.; Budinger, J. M.; Brown, G. B. *J Natl ncer Inst* 61(6): 1411-1414; 1978.

ts exposed directly or transplacentally to N-oxide 3-hy- oxyxanthine (3-OH-X) developed mammary tumors at sig- icantly increased rates over controls. Among female Wi- r rats that received 3-OH-X sc 1x/wk in varying doses, ginning at age 9 days, 4 wk, or 10 wk, there was a signifi- ntly increased proportion of animals bearing mammary tu- ors and an increased number of tumors/rat in all dose oups except the highest (7 mg x 22). In that group, the rats ed before mammary tumors could develop. Histologically, e tumors included fibroadenomas, adenomas, and car- nomas. Administration of 3-OH-X to males sc or to females did not increase mammary tumor incidence. Female off- ring of Sprague-Dawley mothers given four ip injections 25 mg 3-OH-X during pregnancy developed mammary mors significantly more often than controls (93% vs. 57%). ne number of tumors/rat was also significantly increased, t the number of females with at least one malignant mam- ary tumor (3/14) was similar to that in control group /16). Lower prenatal doses of 3-OH-X did not increase male mammary tumor incidence, but male tumor incidence as greater than the control incidence in all dose groups. ecause the tumors initiated by transplacental exposure tc OH-X remained dormant for many months, prolactin may ve stimulated their growth as the rats aged. (19 refs)

8-6251 **Excretion and Distribution of Morpholine Salts in Rats.** (Eng) Tanaka, A. (Dept. Medical hemistry, Natl. Inst. Hygienic Sciences, 18-1, Kamiyoga chome, Setagaya-ku, Tokyo, Japan); Tokieda, T.; Nam- aru, S.; Osawa, M.; Yamaha, T. *J Food Hyg Soc Jpn* 19(3): 29-334; 1978.

he elimination, organ distribution, and metabolism of mor- holine HCl (MPL HCl) and MPL palmitate were studied male Wistar rats by chemical assays using gas-liquid romatography and by radioassays using ^{14}C-MPL. For the nemical assay, the MPL HCl doses were 500 mg/kg po and 250 mg/kg iv; for the radioassays, the doses were 200 mg/kg po and 150 mg/kg iv. ^{14}C-MCL palmitate (400 mg/kg) was given po through a stomach tube. MPL HCl was eliminated very rapidly after po and iv administration. In the chemical assays, >85% appeared in urine after 24 hr, and 90% was excreted over 3 days. Very small amounts were excreted in feces. Similar results were obtained for both salts by radioas- say. Over 5 days, 80%-90% was excreted in urine and 3%-10% in feces, with fecal excretion of the palmitate being slightly higher than that of the HCl. Thin-layer chromatogra- phy confirmed that MPL was excreted unchanged. MPL ac- cumulated primarily in muscle and intestine, and significant quantities remained in the intestine for 12 hr. Elimination from other organs was very rapid. Adipose tissue showed the lowest affinity for MPL, regardless of route of administra- tion. From these findings, it would appear that MPL is an inert substance in the rat body. (15 refs)

78-6252 **Chromosome Investigations on Workers Exposed to Styrene/Polystyrene.** (Eng) Thiess, A. M. (Occupational Medicine and Health Protection, BASF Aktiengesellschaft, 6700 Ludwigshafen/Rhein, W. Germany); Fleig, I. *J Occup Med* 20(11): 747-749; 1978.

Cytogenetic studies were carried out in 12 chemical plant employees with 3-39 yr possible exposure to styrene, and uri- nary mandelic acid levels were studied in 58 additional em- ployees. The frequency of aberrant metaphases in the chromosomes of the 12 workers studied was 1.9%; this fre- quency was the same as that in 12 controls. Forty-eight work- ers excreted <30 mg/liter mandelic acid in the urine; 8 ex- creted 30-50 mg/liter, and only 2 excreted >50 mg/liter. The concentratons of sytrene at the plant were usually <1 ppm; in areas where the concentrations were higher, but <10 ppm, exposure lasted only 3-5 min at a time. (9 refs)

78-6253 **Mutagenicity of Styrene and Styrene Oxide in Drosophila Tests (Meeting Abstract).** (Eng) Sorsa, M. (Dept. Genetics, Univ. Helsinki, Helsinki, Fin- land); Laamanen, I.; Vainio, H. *Mutat Res* 53(2): 266-267; 1978. (no refs)

78-6254 **Carcinogenicity and Mutagenicity of 5-Ni- troacenaphthene and Tetrachlorobenzidine.** (Eng) Takemura, N. (Dept. Public Health, Jikei Univ. Sch. Medicine, Tokyo, Japan); Hashida, C.; Shimizu, H. *In: Pre- vention and Detection of Cancer. Proceedings of the Third In- ternational Symposium on Detection and Prevention of Cancer Held by the International Study Group for the Detection and Prevention of Cancer in New York, April 26 - May 1, 1976.* International Study Group for the Detection and Prevention of Cancer. (New York, NY): Vol. 2(Part 1), 2404 pp.; 1329-1336; 1978.

The carcinogenicity of 5-nitroacenaphthene (NAN) and tetrachlorobenzidine (TCB) was tested in male and female Wistar rats and Syrian golden hamsters and in female dd strain mice; their mutagenicity was tested on *Salmonella typhimurium* strains TA100 and TA98. Twelve of 30 female rats given NAN (1% of diet for 4 mo) lived >200 days after the start of feeding and developed malignant tumors: 1 rhabdomyosarcoma, 2 sebaceous squamous cell carcinomas in the ear duct, 5 intraductal breast carcinomas, and 10 adenocarcinomas of the small intestine. Ten of 20 female rats given NAN (1% of diet for life) lived >200 days and developed tumors in the ear duct (4), breast (3), kidney (1), and liver (1). Thirteen of 24 female hamsters given NAN (1% of diet for 6 mo) survived >270 days, and 7/13 developed cholangiomas. None of the males developed tumors. Seventeen of the 20 mice given TCB (0.1% of diet for life) survived >300 days and developed 14 malignant lymphomas, 2 mammary carcinomas, and 1 mammary fibrosarcoma. Both chemicals were mutagenic on *S. typhimurium* TA100 and TA98 with metabolic activation. Precautions should be taken when these chemicals are handled occupationally. (4 refs)

78-6255 **Cytological Effects of the Antihelminthic Agent Oxyclozanide on Mitotic Chromosomes of *Allium cepa* L.** (Eng) Reddy, P. V. (Dept. Zoology, Kakatiya Univ., Vidyaranyapuri Warangal 506 009, India); Murthy, D. K.; Subramanyam, S. *Indian J Exp Biol* 15(1): 1073-1074; 1977.

The effect of the antihelminth oxyclozanide (Zanil, or 3,3,5,5,6-pentachloro-2,2-dihydroxybenzanilide) on *Allium cepa* roots soaked in a 0.25% soln of the agent for 2-24 hr was determined. There was a gradual decline in the mitotic index with time, with the most intense effect being observed around 24 hr. A pronounced C-mitotic effect and chromosome abnormalities were also induced. The mitotic index rose slowly and the percentage of abnormal cells decreased when the roots were allowed to recover for 24, 48, and 72 hr after an 8-hr treatment, indicating the reversibility of the genetic damage. (14 refs)

78-6256 **Potential Carcinogenicity of Some Food Preservatives in the Presence of Traces of Nitrite (Meeting Abstract).** (Eng) Khoudokormoff, B. (Lab. Microbial Genetics, Res. and Development, P.O. Box 1, Delft, Netherlands); Gist-Brocades, N. V. *Mutat Res* 53(2): 208-209; 1978. (no refs)

78-6257 **Enhancement of Liver Microsome Epoxide Hydratase Activity in Rodents by Treatment with 2(3)-*tert*-Butyl-4-hydroxyanisole.** (Eng) Cha, Y. N. (Dept. Pathobiology, Johns Hopkins Medical Inst., Baltimore, MD, 21205); Martz, F.; Bueding, E. *Cancer Res* 38(12): 4496-4498; 1978.

Epoxide hydratase (EH) activity was assayed in liver m crosomes from female CD-1 mice fed a diet containing 0.75 of the antioxidant 2(3)-tert-butyl-4-hydroxyanisole (BH for 10 days. The liver microsomes were incubated with st rene oxide [200 nanomoles (nmol)], and EH activities we expressed in terms of nmol of styrene diol metabolite per m protein per min. Three days after initiation of BHA feedin the specific activity of EH was 9.40 nmol diol/mg/protein min, or 9 x the control value. The activity then rose mo slowly, reaching 11.11 nmol/mg/protein/min at 10 day Only two- to threefold increases in enzyme activity were i duced by 3-methylcholanthrene, phenobarbital, and Aroc 1254. When BHA (750 mg/kg/day) was administered by ga tric intubation for 4 days, the increase in EH activity w 75% of that attained by dietary administration of the antio dant. The possibility that BHA may enhance or prote against the carcinogenic effects of diol-epoxides is discusse (26 refs)

78-6258 **N-Acetyl-β-glucosaminidase Activity in t Peripheral Blood WBC of Rats Subacutely E posed to Benzene Vapor.** (Pol) Starek, A. (Katedra Medyc ny Pracy i Chorob Zawodowych, AM w Krakowie, 30-9 Krakow 28, Poland); Moszczynski, P. *Patol Pol* 29(1): 71-7 1978.

The effect of a 10-day exposure to benzene vapor (6 hr/da 27,000 mg/m³) on N-acetyl-β-glucosaminidase (AGA) a tivity in the peripheral blood WBC was studied in 12 ma Wistar rats aged 8 mo. The exposure reduced the number neutrophil granulocytes from 3,826/mm³ to 2,271/mm³ ($p < 0.005$), the AGA activity in the granulocytes from 53.8 16.8 units ($p < 0.001$), the lymphocyte count fro 10,963/mm³ to 1,330/mm³ ($p < 0.001$), and the percenta of AGA-positive lymphocytes from 54.9% to 50.4% ($p < 0.05$). Within the subpopulation of AGA-positive ly phocytes, the percentage of granular-type cells decreased a that of granular-diffusion and diffusion-type cells increase The effects are due to the damaging action of benzene on t granulocyte lysosomes and on peripheral blood lymphocyte (24 refs)

78-6259 **Modified Method for Electron Captu Gas-Liquid Chromatographic Determination Hexestrol Residues in Bovine Tissues.** (Eng) Tobioka, H (Dept. Animal Science, Coll. Agriculture, Kyoto Univ Kyoto 606, Japan); Kawashima, R. *J Assoc Off Anal Che* 61(5): 1054-1057; 1978.

Hexestrol residues in the tissues of cows injected with hexe trol dicaprylate were determined by electron capture gas-li uid chromatography. The method was suitable for determi ing residues of 0.5 ppb; the limit of sensitivity ranged fro 0.1 to 0.2 ppb. (16 refs)

260 **Thiophene Analogues of the Carcinogens Benzidine and 4-Aminobiphenyl: Evaluation In Vitro.**) Ashby, J. (Central Toxicology Lab., Imperial Chemical stries Ltd., Alderley Park, Macclesfield, Cheshire, En-d); Styles, J. A.; Anderson, D.; Paton, D. *Br J Cancer*): 521-529; 1978.

thiophene analogs of benzidine and 4-aminobiphenyl acetamidophenyl-2-thiophenamine hydrochloride I), 5-phenyl-2-thiophenamine hydrochloride (VIX), -p-acetamidophenylthiophen-2-yl)acetamide (XV), and -phenylthiophen-2-yl)-acetamide (XVI), were tested for inogenicity in vitro by the Ames reverse-mutation assay the Styles cell-transformation assay. In Ames tests with *monella typhimurium* strains TA1535, TA1538, TA98, TA100, each of the thiophenes produced at least one tive response in TA1538 or TA98, sometimes in the ab-e of a rat liver S-9 mix. In two runs of the Styles assay, acetyl derivatives XV and XVI gave a positive response, the amine hydrochlorides XIII and XVI were negative. n the acetyl derivatives possessed greater cytotoxicity. It ggested that the relative transforming abilities of these pounds is determined by the ability of XV and XVI to n DNA-reactive hydroxylamine-ester compounds and the ility of XIII and XIV to form N-hydroxy-ester com-nds. (29 refs)

261 **Di-(4-aminophenyl)-methane (MDA): 4-7 Year Dog Feeding Study.** (Eng) Deichmann, W. B. s. and Teaching Center Toxicology, Dept. Pharmacology, iv. Miami Sch. Medicine, P.O. Box 248216, Coral Gables, , 33124); MacDonald, W. E.; Coplan, M.; Woods, F.; m, E. *Toxicology* 11(2): 185-188; 1978.

e possible carcinogenic action of purified and crude 4-aminophenyl)-methane (MDA) on the urinary bladder s studied in nine female beagle dogs. The compounds were en po at a dose of 70 mg/kg/day 3 x/wk for life (up to r and 2 mo). There were no significant effects on body wt ept for an occasional wt loss that was followed by quick overy after withdrawal from treatment. Results of all oratory tests were negative except for elevated alkaline sphatase activity in two dogs. Moderate to severe gross cropathologic changes occurred in the livers of all dogs; severe changes were seen in the kidneys (4 dogs), spleens urinary bladders (2), lungs (3), ovaries and fallopian tubes and uterus (1). There were no tumors of the urinary dder or liver. (3 refs)

-6262 **Chlorination of Benzidine and Other Aromatic Amines in Aqueous Environments.** (Eng) Jen-ns, R. L. (County Sanitation Districts Los Angeles County, n Jose Creek Water Quality Lab., 1965 S. Workman Mill ad, Whittier, CA, 90601); Haskins, J. E.; Carmona, L. G.; ird, R. B. *Arch Environ Contam Toxicol* 7(3): 301-315; 78.

Exposure of aniline, but not N,N-dimethylaniline, to chlorinated waters yielded a solid product. For these monophenyl amines, ring chlorination was a significant depletion pathway. Extended chlorination of benzidine resulted immediately in a solid product that, upon infrared analysis, was shown to be a polymeric structure with no ring chlorination. Analysis of the supernatant revealed no ring-substituted isomers of benzidine. (18 refs)

78-6263 **An Improved Method for Detecting Mutagens (Meeting Abstract).** (Eng) Yahagi, T. (Natl. Cancer Res. Inst., Tokyo, Japan); Nagao, T.; Matsushima, T.; Seino, Y.; Sawamura, N.; Shirai, A.; Kawachi, T.; Sugimura, T. *Mutat Res* 53(2): 285; 1978. (no refs)

78-6264 **Genetic Variation in N-Acetylation of Carcinogenic Arylamines by Human and Rabbit Liver.** (Eng) Glowinski, I. B. (Dept. Pharmacology, Univ. Michigan, Ann Arbor, MI, 48109); Radtke, H. E.; Weber, W. W. *Mol Pharmacol* 14(5): 940-949; 1978.

The arylamine carcinogens aminofluorene, α-naphthylamine, β-naphthylamine, benzidine, and methylene bis-2-chloroaniline were found to be acetylated by the same polymorphic N-acetyltransferase (NAT) as sulfamethazine (SMZ) and isoniazid (INH). Liver (0.10 ml) NATs purified from slow and fast INH-acetylator rabbits and humans were incubated with 0.05 ml aqueous radioactive acetyl coenzyme A (2×10^{-3} M) and 0.05 ml amine substrate soln. After the radioassay of acetylating activity, Km values were determined for enzyme-substrate interactions. Rabbit liver NAT had a smaller apparent Km than the human liver enzyme for all substrates tested except α and β naphthylamine, and reactions with carcinogenic substrates in both enzyme systems yielded Km's at least an order of magnitude smaller than when SMZ was the substrate. Although Km values within a species did not change, the carcinogenic compounds showed greater differences in acetylation rates between rapid and slow acetylators than did SMZ; therefore, they appeared to be polymorphically acetylated in both rabbit and man. Octanol-water partition coefficients measured for each substrate correlated closely with the apparent Km values for both human and rabbit NAT, supporting the hypothesis that differences in apparent Km's were related to the greater hydrophobicity of the carcinogens than of SMZ. Because all the carcinogens served as substrates for polymorphic NAT, hydrophobicity and differences between slow and fast acetylators could be important in determining an individual's susceptibility to arylamine carcinogenesis. (51 refs)

78-6265 **Hepatocarcinogen-induced tRNA Methylase Activity in Rat Liver.** (Eng) Forrester, P. I. (Div. Medical Biochemistry, Faculty Medicine, Univ. Cal-

gary, Calgary, Canada); Hancock, R. L. *Physiol Chem Phys* 10(2): 115-123; 1978.

Dimethylaminoazobenzene and carbon tetrachloride extend the list of hepatocarcinogens capable of increasing rat liver transfer RNA (tRNA) methylase activity. Ethionine increased this activity in rats and guinea pigs but not in chicks. Aminoazobenzene, acetylaminofluorene, α- and β-naphthylisothiocyanate, dimethyl- and diethylnitrosamine, and methylcholanthrene produced no increase or slight increases. (13 refs)

78-6266 **Toxicity of p-Substituted Derivatives of Aniline in Experimental Rats.** (Cze) Matrka, M. (Toxikol. Odd., Vyzkumny ustav organickych sintez, 533 51 Pardubice-Rosice, Czechoslovakia); Rambousek, V.; Zverina, Z. *Cesk Hyg* 23(4): 168-172; 1978.

The acute po toxicity of aniline and six of its substituted derivatives was determined in male Wistar rats. The substances were administered in soln or in an olive oil suspension. The LD_{50} values were 0.440 mg/kg for aniline (A), 0.417 mg/kg for 4-fluoroaniline (FA), 0.370 mg/kg for 4-chloroaniline (CA), 0.456 mg/kg for 4-bromoaniline (BA), 0.523 mg/kg for 4-iodoaniline (IA), 0.794 mg/kg for 4-methylaniline (MA), and 0.750 mg/kg for 4-nitroaniline (NA). The mole LD_{50} values were 0.00265 (BA), 0.00239 (IA), 0.00755 (MA), and 0.00543 (NA). Hammett's σ constants were 0 (A), +0.06 (FA), +0.23 (CA and BA), +0.27 (IA), -0.17 (MA), +0.78 (NA). A good correlation was seen between the mole LD_{50} values and Hammett's constants. The six aniline derivatives represent the last biotransformation step of the corresponding carcinogens derived from 1-phenyl-3,3-dimethyltriazene. (16 refs)

78-6267 **Metabolism-mediated Cytotoxicity of Chemical Carcinogens and Non-carcinogens.** (Eng) Wiebkin, P. (Inst. Industrial, Environmental Health and Safety, Univ. Surrey, Guildford, Surrey GU2 5XH, England); Fry, J. R.; Bridges, J. W. *Biochem Pharmacol* 27(14): 1849-1851; 1978.

The general applicability of a mixed cell culture system in assessing the importance of metabolism in chemically mediated cytotoxicity was tested using carcinogenic and noncarcinogenic chemicals. Rat fibroblasts were incubated with at least five concentrations of each test compound for 1 hr at 37 C in the presence or absence of viable rat hepatocytes. The samples were then diluted and cultured at 37 C for 6-8 days, after which time counts of nuclei were performed and the results calculated as ID_{50} values; i.e., the concentration of the chemical that inhibited fibroblast growth by 50%. In the presence of hepatocytes, the most toxic pair of compounds tested was 3′-methyl -4- dimethylaminoazobenzene (3′-methyl-DAB; ID_{50}, 0.1 μg/ml) and 2-methyl -4- dimethylaminoazobenzene (2-methyl-DAB; ID_{50}, 2.0 μg/ml). the absence of hepatocytes, the ID_{50} values for 3′-me yl-DAB and 2-methyl-DAB were > 125 and > 250 μg/ respectively. Mitomycin C also required hepatocyte metal lism for its cytotoxicity to be fully expressed, but hepatoc metabolism decreased the cytotoxicity of 4-nitroquin line-1-oxide. Other compounds that showed increased cy toxicity in the presence of hepatocytes were cyclophospl mide, dimethylnitrosamine, 2-acetylaminofluore 4-acetylaminofluorene, 6-aminochrysene, and 2-aminoch sene. (14 refs)

78-6268 **Mutagenicity of the Herbicide Trifluralin *Drosophila melanogaster* (Meeting Abstrac** (Eng) Murnik, M. R. (Dept. Biological Sciences, Weste Illinois Univ., Macomb, IL, 61455). *Mutat Res* 53(235-236; 1978. (1 ref)

78-6269 **Mutagenicity of Six Indian Hair Dyes Test in *Salmonella typhimurium* Strains (Meeti Abstract).** (Eng) Bajaj, M. H. (Biology and Agriculture Di Bhabha Atomic Res. Centre, Bombay-400 085, India); No ni, N. K. *Mutat Res* 53(2): 149-150; 1978. (no refs)

78-6270 **Liver and Urinary Bladder Tumors in Do from 3,3′-Dichlorobenzidine.** (Eng) Stula, E. (Haskell Lab., Elkton Road, Newark, DE, 19711); Barn J. R.; Sherman, H.; Reinhardt, C. F.; Zapp, J. A. *J Envir Pathol Toxicol* 1(4): 475-490; 1978.

The carcinogenic effects of po 3,3′-dichlorobenzidine (DC were studied in six female beagle dogs. DCB was given a rate of 100 mg 3x/wk for 6 wk, then 5x/wk for up to 7.1 Untreated controls were sacrificed after 8.3-9.0 yr. DCB-treated dogs showed elevated plasma glutamic-pyru transaminase activity during the first 3 yr, and two do showed elevated activity throughout the test. One DCB do sacrificed in extremis after 3.5 yr, had no tumors. Anoth sacrificed in extremis after 6.6 yr, had an undifferentiat carcinoma of the liver with metastases to many organs a a papillary transitional cell carcinoma of the urinary bladd Three of the remaining four dogs sacrificed after 7.1 yr h hepatocellular carcinomas, and all four had transitional c carcinomas of the urinary bladder. There were no such t mors in the control dogs. The data indicate that DCB is ca cinogenic for the liver and urinary bladder in the dog and th in this species, it is more carcinogenic than benzidine. (refs)

78-6271 **Mutagenicity of Pesticides in Blue-Green A gae.** (Eng) Das, B. (Lab. Blue-Green Alga

tral Rice Res. Inst., Cuttack 753006, Orissa, India); gh, P. K. *Microbios Lett* 5(19/20): 103-107; 1977.

e mutagenicity of hexachlorocyclohexane (BHC) and dichlorophenoxyacetic acid (2,4-D) to four blue-green al- (3 N-fixing, 1 non-N-fixing) was investigated. A slight rease in mutation frequency was noticed after treatment h BHC, but 2,4-D treated cultures did not show any in- ase. The results suggest that BHC is a weak mutagen for e-green algae, whereas 2,4-D is nonmutagenic. (19 refs)

6272 **The Mutagenicity of Substituted and Unsubstituted Styrene Oxides in *E. coli*: Relationship tween Mutagenic Potencies and Physico-chemical Proper-s.** (Eng) Sugiura, K. (Inst. Ecotoxicology, Gakushuin iv., Toshima-ku, Tokyo 171, Japan); Yamanaka, S.; kasawa, S.; Goto, M. *Chemosphere* 7(9): 737-742; 1978.

e relationship between the mutagenic potencies and ysicochemical properties of substituted and unsubstituted rene oxides was studied. 3,4-Dimethylstyrene oxide was st lethal to *Escherichia coli* strain WP100 and more muta- ic in strains WP100 and CM571 than in strains WP2uvrA d WP2. Styrene oxide had similar lethal and mutagenic ects. These results indicate that the uvrA and recA genes ect both the lethal and mutagenic responses. The tagenicity and lethality of these and other compounds in- ased in the order: m-methoxystyrene oxide < styrene ox- < p-methylstyrene oxide < m-methylstyrene oxide < -dimethylstyrene oxide < m-chlorostyrene oxide < promostyrene oxide. In reactions of substituted styrene ox- s with nucleophiles, the normal reaction rate was higher th electron-withdrawing substituents and lower with elec- n-releasing substituents. In contrast, the rate of abnormal actions (attack at CH) was higher with electron-releasing bstituents. The relative LD_{50} values of the styrene oxide rivatives agreed with the relative partition coefficients, sug- sting that the rate of transport of styrene oxides to their llular sites of action is the rate-limiting condition. The data monstrate that the mutagenic effect of a chemical may vary th the structure of its products. (11 refs)

-6273 **Pathology of Esophageal Neoplasms and Associated Proliferative Lesions Induced in Rats y N-Methyl-N-benzylnitrosamine.** (Eng) Stinson, S. F. (Tu- or Pathology Branch, Div. Cancer Cause and Prevention, CI, NIH, Public Health Service, U.S. Dept. Health, Educa- n and Welfare, Bethesda, MD, 21205); Squire, R. A.; born, M. B. *J Natl Cancer Inst* 61(6): 1471-1475; 1978.

fter receiving 20 weekly sc injections of N-methyl-N-ben- lnitrosamine (MBZN: 2.5 mg/kg), 24 inbred male F344 ts developed 194 lesions of the upper gastrointestinal tract. Grossly, most lesions were exophytic; 74% were pedunculated papillary growths and the remainder were sessile proliferations. Localized elevated thickening of the esophageal wall was observed in 20% of the rats. All rats developed papillomas, 63% developed carcinomas that invaded the esophageal wall, and 67% developed pedunculated papillary carcinomas. Of the esophageal tumors, 66% were papillomas, 17% were pedunculated papillary carcinomas, and 17% were invasive carcinomas. The papillomas were pedunculated (87%) or sessile (13%). The carcinomas that invaded the esophageal wall were sessile (78%) or infiltrating (22%). All neoplasms were well-differentiated squamous cell tumors, with varying degrees of keratinization. Although penetration through the esophageal wall was common, no metastases were seen. No primary lesions were seen in sites other than the esophagus and pharynx. These tumors were similar morphologically to human specimens. Therefore, the usefulness of this model in the study of human esophageal carcinoma is indicated. (11 refs)

78-6274 **The Role of Glutathione in Experimental Chemical Hepatocarcinogenesis.** (Eng) Fiala, S. (Cell Physiology Lab., VA Center, Martinsburg, WV); Trout, E. C.; Kettering, W. G. *In: Prevention and Detection of Cancer. Proceedings of the Third International Symposium on Detection and Prevention of Cancer Held by the International Study Group for the Detection and Prevention of Cancer in New York, April 26 - May 1, 1976.* International Study Group for the Detection and Prevention of Cancer. (New York, NY): Vol. 2(Part 1), 2404 pp.; 1291-1304; 1978.

The behavior of glutathione (GSH) in rat liver during azo dye-induced carcinogenesis was investigated to determine whether hepatocarcinogenesis is due to inhibited and disrupted differentiation of stem cells. The concentration of GSH in fetal and neonatal liver was 110 and 140 mg/100 g, respectively, vs 234 mg/100 g in adult liver. Following administration of 3′-methyl-4-dimethylaminoazobenzene (3′-Me-DAB; 33 mg), there was a small initial decrease in liver GSH due to its conjugation with some of the azo dye metabolites and its elimination in bile. This was followed by a rapid increase in GSH synthesis as early as 8 hr after 3′-Me-DAB administration. In later stages of hepatocarcinogenesis, γ-glutamyltranspeptidase (GT-ase) activity was very high, resulting in rapid degradation of GSH. The liver of hypophysectomized rats, which do not develop hepatomas as a result of azo dye administration, did not form GSH conjugates and did not have increased GSH or GT-ase activity. GSH, being nucleophilic, may combine with and protect against various electrophilic metabolites. Even with an excess of carcinogen, the hepatocyte seems to be largely immune to electrophilic attack because the initial GSH depletion is overcompensated by its increased rate of synthesis. The mature hepatocyte, therefore, does not appear to be the target of proximate carcinogens. A fetallike hepatic stem cell with high GT-ase activity may be the actual carcinogen-sensitive cell. (27 refs)

78-6275 **Inhibition of 3′-Methyl-4-dimethylaminoazobenzene-induced Hepatocarcinogenesis by Portacaval Shunt.** (Eng) Fiala, S. (Cell Physiology Lab., Veterans Admin. Center, Martinsburg, WV, 25401); Pragani, B.; Reuber, M. D. *Tumori* 64(2): 131-142; 1978.

Adult male Sprague-Dawley rats who underwent an end-to-side portacaval shunt (PCS) did not develop hyperplastic nodules and hepatomas when they were fed 3′-methyl-4-dimethylaminoazobenzene (3′-Me-DAB) in a semisynthetic basal diet for up to 169 days. In contrast, all intact rats fed the same diet for only 75 days developed hyperplastic nodules. Following transfer to a normal diet for another 25 days, hepatomas developed in 100% of these animals. The amount of protein-bound 3′-Me-DAB and the glutathione (GSH) level was lower in operated rats than in intact controls. A single large dose of 3′-Me-DAB (10 mg/100 g) increased the GSH concentration by only 30% after 24-48 hr, compared with an increase of 50%-100% in intact rats. There was no gradual increase in the activity of γ-glutamyltranspeptidase (GTase) in operated rats during 5.5 mo of 3′-Me-DAB feeding. The increase in GTase activity was never >30% higher than the level in livers of operated rats fed a basal diet without the carcinogen. This striking inhibition of GTase activity induced by 3′-Me-DAB in PCS-operated rats contrasted with a 5,000% increase in enzyme activity found in the livers of intact rats with hyperplastic nodules after 75 days of 3′-Me-DAB feeding and with the up to 10,000% increase in the hepatomas. These effects and the inhibition of 3′-Me-DAB-induced hepatocarcinogenesis, manifested by a lack of preneoplastic morphologic changes and the absence of hepatomas in rats after PCS, can best be explained by a functional deficiency of the liver to metabolize the procarcinogen 3′-Me-DAB to an activated carcinogen. (25 refs)

78-6276 **A Study of Cyclic Nucleotide Metabolism and the Histology of Rat Liver During 3′-Methyl-4-dimethylaminoazobenzene Carcinogenesis. I. Histology.** (Eng) Boyd, H. (Dept. Pharmacology, Univ. Miami Sch. Medicine, Miami, FL, 33152); Hensley, G. T. *Tissue Cell* 10(3): 463-476; 1978.

Male Sprague-Dawley albino rats were fed 3′-methyl-4-dimethylaminoazobenzene (3′-MeDAB) ad libitum in pellets (0.06% in 0.75% corn oil) for 12 wk, and their livers were examined histologically at weekly intervals up to 13 wk. The first tumor mass was noted at 4 wk and there was a 100% incidence of cholangiocarcinomas by 10 wk. Acidophilic hepatocytes that appeared in periportal regions of liver lobules at 3 wk were smaller than normal and glycogen-deficient. After 4 wk, even smaller glycogen-deficient cells with a large nucleus/cytoplasm ratio appeared. These small cells and the acidophilic cells underwent mitosis, and there was no indication of acute or chronic inflammation or fibrosis. By 7 wk, the small cells became increasingly organized into ductular structures that were composed of columnar epithelial cells and mucous-secreting goblet cells. Proliferating epithelial cells were frequently associated with necrosis and c struction of the parenchyma. Tissue that appeared to uninvolved to the naked eye often contained 50% unorga ized small cells. In this study, no hepatocellular carcinom developed by 13 wk. (42 refs)

78-6277 **Pre-tumor Phase Serum Alpha-Fetoprotein a Its Molecular Variants During Hepatocarcin genesis.** (Eng) Nadworny, H. A. (Dept. Medicine, Univ. V mont Coll. Medicine, Burlington, VT, 05401); Smith, C. Kelleher, P. C. *In: Prevention and Detection of Cancer. P ceedings of the Third International Symposium on Detecti and Prevention of Cancer Held by the International Stu Group for the Detection and Prevention of Cancer in N York, April 26 - May 1, 1976.* International Study Group f the Detection and Prevention of Cancer. (New York, NY Vol. 2(Part 1), 2404 pp.; 1283-1290; 1978.

Radial immunodiffusion was used to monitor the week serum alpha-fetoprotein (AFP) concentrations in 39 Fisch 344 rats that were fed 0.063% 3′-methyl-4-dim thylaminoazobenzene (3′-Me-DAB) in the diet beginning 6 wk of age. Serum AFP levels were undetectable (< μg/ml) at 6 wk of age. AFP was detectable in the serum 30/39 rats after 3 wk of 3′-Me-DAB intake and in all surviving rats after 6 wk of intake. This first elevation pre-tumor phase serum AFP lasted until 7 wk after the sta of the diet and was followed by a second elevation startin at 10-11 wk in 35/36 rats and lasting for 4-6 wk. Max seru AFP concentrations during each period of increase vari widely among the individual rats (12-700 μg/ml in the fir period, 20-220 μg/ml in the second). The percentages of tot pre-tumor phase serum AFP not reactive with concanaval A showed no consistent pattern either within an individu animal (14%-51%) or among individuals (11%-51%). Th mechanisms responsible for the cyclic elevations of pre-tum phase serum AFP are not known. (13 refs)

78-6278 **Mechanisms of Immunosuppression Induced Mice by o-Aminoazotoluene and Its Nonca cinogenic Analog.** (Rus) Kaledin, V. I. (Lab. Cancer Gene ics, Inst. Cytology and Genetics, Siberian Branch, Aca Sciences USSR, Novosibirsk, USSR); Glazko, T. T.; Kras P. M.; Chesnokova, V. M. *Vopr Onkol* 24(9): 46-52; 1978

The immunosuppressive effects of single ip doses o-aminoazotoluene (OAT: 4.5 mg) or its noncarcinogen analog aminoazobenzene (AAB: 4 mg) were studied in mal DD mice inoculated im with 10^6 Krebs-2 carcinoma cell When OAT and AAB were administered 24 hr before tumo transplantation, tumor wts at the end of the experiment wer 0.68 and 0.9 g, respectively, vs 0.55 g in controls. When OA and AAB were injected 72 hr before tumor graft, tumor wt were 1.36 and 1.26, respectively, vs 0.91 g in controls. Immu nization of the mice with irradiated (10,000 rads) tumor cell

ngly inhibited the growth of the implanted tumor, but the ıor wt was 3-3.5 times higher in the immunized and OAT-AAB-treated animals than it was in immunized animals hout OAT or AAB treatment. The findings indicate the hly pronounced immunosuppressive effect of OAT and B. The immunosuppressive effect of AAB was due to its phocytotoxicity, whereas the effect of OAT was mediated the adrenal gland. After OAT injection, the serum oxycorticosteroid level was elevated, although production his hormone by the adrenal glands was not increased. The umulation of glucocorticoids in serum after OAT injection elieved due to reduced hormone utilization because of a ck of receptor proteins or metabolizing hepatic enzymes the carcinogen. (12 refs)

-6279 **The Generation of Aerosols of Carcinogenic Aromatic Amines.** (Eng) Rappaport, S. M. (Sch. blic Health, Univ. California, Berkeley, CA, 94720); ttemy, D. J. *Am Ind Hyg Assoc J* 39(4): 287-294; 1978.

ıe development of an aerosol generator for the production test atmospheres of carcinogenic aromatic amines is de-ribed. The generator, a compressed-gas nebulizer, operates a temperature above the melting point of the test com-unds and uses nitrogen as a driving force. The nebulizer tput and size distributions of aerosols of 4,4′-me-ylenebis(2-chloroaniline), benzidine, and 3,3′-dichloroben-dine are given. The apparatus is capable of continuous oper-ion over a minimum of 8 hr. (13 refs)

3-6280 **Mutagenicity Studies of Commercially Available Saccharins (Meeting Abstract).** (Eng) ajumdar, S. K. (Dept. Biology, Lafayette Coll., Easton, A, 18042); Viglianti, G. A.; Thatcher, J. D.; Dennis, E. H.; aharam, L. C.; Natoli, J. *Can J Genet Cytol* 20(3): 449; 78. (no refs)

8-6281 **Absorption of Saccharin from Rat Urinary Bladder (Letter to Editor).** (Eng) Colburn, W. . (Dept. Biochemistry and Drug Metabolism, Hoffmann-La oche, Inc., Nutley, NY, 07110). *J Pharm Sci* 67(10): 493-1494; 1978.

Measurements of plasma levels of saccharin following in vivo nstillation of 10 μg or 1 or 100 mg/kg of the compound into he urinary bladder of male Sprague-Dawley rats showed that his substance was absorbed extensively from the bladder. ignificant reabsorption may decrease the elimination rate for accharin in much the same way as enterohepatic cycling and robably accounts for the retention of saccharin in urinary ladder tissue. (3 refs)

78-6282 **Saccharin Inhibits Guanylate Cyclase Activity: Possible Relationship to Carcinogenesis.** (Eng) Vesely, D. L. (Dept. Medicine, Univ. Miami Sch. Medicine, Miami, FL, 33152); Levey, G. S. *Biochem Biophys Res Commun* 81(4): 1384-1389; 1978.

The effect of saccharin (2,3-dihydro-3-oxobenzisosulfonazole) on guanylate cyclase activity was tested in a variety of tissues obtained from male Sprague-Dawley rats. Saccharin significantly inhibited guanylate cyclase in urinary bladder, liver, stomach, colon, and kidney tissues over the concentration range 16-160 mM. Maximum inhibition was 60%-75%. The concentrations of saccharin decreasing guanylate cyclase activity in the in vitro rat urinary bladder assay (approx 3 to 9 mg/ml) were well within the range of concentration which can be obtained in urine of persons who use low calorie soft drinks and sugar substitutes and therefore interact in vivo with bladder tissue The saccharin used in this study was synthesized by the Maumee process and contained no detectable amounts of o-toluenesulfonamide, the impurity most often associated with cancer. It is concluded that the question of saccharin carcinogenicity in man must be seriously studied regardless of its mode of synthesis. (29 refs)

78-6283 **Enhancement of Oncogenesis in C3H/10T1/2 Mouse Embryo Cell Cultures by Saccharin.** (Eng) Mondal, S. (Comprehensive Cancer Center, Univ. Southern California, Los Angeles, CA, 90033); Brankow, D. W.; Heidelberger, C. *Science* 201(4361): 1141-1142; 1978.

The transforming and promoting activities of saccharin were studied in vitro using C3H/10T1/2, clone 8, mouse embryo fibroblasts. At 2 mg/ml, saccharin alone was nontoxic and nontransforming, and it had no initiating effect when followed 4 days later by continuous treatment with 12-O-tetradecanoylphorbol-13-acetate (TPA). However, both pure and impure samples of saccharin (100 μg/ml) showed significant cocarcinogenic activity during continuous treatment of cultures initiated with 3-methylcholanthrene (0.1 μg/ml). TPA, but not saccharin, promoted UV-initiated cells. The reason for this difference between these otherwise equivalent initiators is not clear. Nevertheless, the results suggest that saccharin acts as a promoter and that caution should be applied to the indiscriminate or long-term use of saccharin in human nutrition. (22 refs)

78-6284 **Cytogenetic Hazards from Fensulfothion, Dexon (DAPA) and its Degradation Product, Dimethylphenylene Diamine (DMPDA) (Meeting Abstract).** (Eng) Panda, B. B. (Cytogenetics Lab., Berhampur Univ., Berhampur 760 007, India); Sahu, R. K.; Sharma, C. B. *Mutat Res* 53(2): 247-248; 1978. (no refs)

78-6285 **On the Mutagenic Action of 2-Methyl-3,5-dinitrobenzamide and 3,5-Dinitrobenzamide (Meeting Abstract).** (Eng) Voogd, C. E. (Natl. Inst. Public Health, PO Box 1, Bilthoven, Netherlands). *Mutat Res* 53(2): 280-281; 1978. (no refs)

78-6286 **Carcinogenicity of o-Aminoazotoluene in Mouse Intestine.** (Rus) Kaledin, V. I. (Lab. Cancer Genetics, Inst. Cytology and Genetics, Siberian Branch, Acad. Sciences USSR, Novosibirsk, USSR); Alekseeva, G. V.; Volkova, A. I. *Biull Eksp Biol Med* 86(10): 476-477; 1978.

The carcinogenicity of o-aminoazotoluene (OAT) was studied in 60 2-mo-old male A/He mice. OAT was implanted under the skin in 8 doses of 10 mg each at monthly intervals (total dose, 80 mg). All animals died 435 ± 13 days after the first implantation. Liver tumors were the principal cause of death, but 19/60 animals also developed intestinal tumors localized exclusively to the cecum. These tumors were identified as adenomas or muciparous adenocarcinomas. According to the literature, A/He mice do not develop spontaneous intestinal tumors, and in previous experiments with CC57BR, C57BL/6, C3H/He, and DD mice treated with OAT in the same manner, intestinal tumors failed to develop. The genetic basis for the sensitivity of the cecal tissue of A/He mice to OAT is unknown. (2 refs)

78-6287 **Mutagenicity of Chlorinated Phenoxyacetic Acids in *Saccharomyces cerevisiae* (Meeting Abstract).** (Eng) Zetterberg, G. (Dept. Genetics and Plant Breeding, Univ. Uppsala, S-750 07, Uppsala, Sweden). *Mutat Res* 53(2): 285-286; 1978. (2 refs)

78-6288 **Case Control Study: Malignant Mesenchymal Soft-Tissue Tumors and Exposure to Phenoxy Acids or Chlorophenols (Letter to Editor).** (Swe) Sandstrom, A. (Umea, Sweden) *Lakartidningen* 75(40):

Fifty-two men, aged 26-80 yr, with malignant mesenchymal soft-tissue tumors and 206 matched controls were surveyed by questionnaire for past occupational exposure to 2,4-dichlorophenoxyacetic acid (2,4-D) and/or 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). The incidence of past exposure was 19/52 among the tumor patients vs 19/206 among the tumor-free controls. This difference was statistically significant ($p < 0.001$). It was not possible to evaluate the risks of 2,4-D and 2,4,5-T separately, because most patients may also have been exposed to other chemicals, such as tetrachlorodibenzodioxin. These findings suggest that exposure to phenoxy acids, chlorophenols, and/or their impurities increases the risk of soft tissue tumors. (5 refs)

78-6289 **The Chemistry of Phenalenium Systems. XX Novel Ring Contraction During m-Chloroperbenzoic Acid Oxidation of Mutag Azuleno[1,2,3-cd]phenalene. A Model for Metabolic Act tion and Binding of Mutagenic Nonalternant Hydrocarl** (Eng) Nakasuji, K. (Dept. Chemistry, Faculty Scie Osaka Univ., Toyonaka, Osaka 560, Japan); Nakamura, Murata, I. *Tetrahedron Lett* (18): 1539-1542; 1978.

The reaction of m-chloroperbenzoic acid azuleno[1,2,3-cd]phenalene (AP), a highly mutagenic, no ternant isomer of benzo(a)pyrene, was investigated. The products formed were 11-oxo-11H-benzo[cd]fluoranth and 1-oxo-1H-benzo[cd]fluoranthene. This reaction may vide a model for the mutagenic and carcinogenic activit AP. (13 refs)

78-6290 **Screening of Safrole, Eugenol, Their Ninhyd Positive Metabolites and Selected Second Amines for Potential Mutagenicity.** (Eng) Green, N. (Dept. Food and Nutrition, Coll. Home Economics, Flor State Univ., Tallahassee, FL, 32306); Savage, J. R. *Mutat* 57(2): 115-121; 1978.

The mutagenicity of safrole (4-allyl-1,2-methylenedioxyb zene), eugenol, the secondary amines with which they c bine during metabolism, and the ninhydrin positive urin metabolites of safrole and eugenol was tested in the di bacterial assay, a microsomal mutagenesis assay (MMA), a host-mediated assay. In the direct bacterial assay, in wh four mutant strains of *Salmonella typhimurium* (TA15 TA1531, TA1532, and TA1964) were used, all the c pounds gave negative results. With the same four mut strains, safrole and its metabolite 3-piperidyl-1-(3′,4′-m thylenedioxyphenyl)-1-propanone were mutagenic w strains TA1530 and TA1532 in the MMA and with stra TA1950 and TA1952 in the host-mediated assay. Dimethy mine was a weak mutagen in the MMA with strain TA15 Negative results were obtained for the safrole metaboli 3-N,N-dimethylamino -1- (3′,4′-methylenedioxyphen 1-propanone and 3-pyrrolidinyl -1- (3′,4′-methyle dioxyphenyl) -1- propanone, eugenol, the euge metabolites 3-piperidyl -1- (3′-methoxy -4′- hydro phenyl)-1-propanone and 3-pyrrolidinyl-1-(3′-metho 4′-hydroxyphenyl)-1-propanone, piperidine, pipec acid, proline, and pyrrolidine in all three assay syste These results suggest that the MMA is more sensit than the host-mediated assay. (16 refs)

78-6291 **Conversion of the N-O-Glucuronide a N-O-Sulfate Conjugates of N-Hydroxyphe acetin to Reactive Intermediates.** (Eng) Mulder, G. J. (La Chemical Pharmacology, Natl. Heart, Lung and Blood Ins NIH, Bethesda, MD, 20014); Hinson, J. A.; Gillette, J. *Biochem Pharmacol* 27(12): 1641-1649; 1978.

stability and reactions of the reactive intermediates ned from phenacetin (PA) N-O conjugates were studied. N-O-glucuronide of ^{14}C-acetyl-N-hydroxy-PA is suffitly stable for it to be purified but slowly degrades in aqueous soln to a reactive intermediate that can covalently bind rotein. Several lines of evidence are given that indicate the major chemically reactive intermediate formed from glucuronidation of N-hydroxy-PA is the deethylated vative, N-acetylimidoquinone. However, the data suggest the formation of PA and 2-hydroxy-PA glucuronide oc- by different mechanisms. The N-O-sulfate of ^{14}C-acet-N-hydroxy-PA also breaks down to a reactive intermediate has properties similar to those of the reactive intermedi- formed from the N-O-glucuronide and thus may also be cetylimidoquinone. In contrast, the relative ability of ious nucleophiles to prevent the covalent binding of the ctive intermediate formed from the N-O-sulfate of cetylaminofluorene to protein differs from the relative lity of the nucleophiles to prevent the covalent binding of reactive intermediate of the N-O-sulfate or the O-glucuronide of PA, suggesting that the relative rates at ich these intermediates combine with the different macnolecules may differ markedly. These studies may be relet to other pathways of activation of PA and acetaminoen. Although the mechanism of PA-induced phrotoxicity is not known, it seems plausible that PA O-glucuronide may play a role, since it would be produced marily in the liver and concentrated in the kidney. Its conrsion to a reactive intermediate, possibly accelerated by the w pH of urine, could lead to covalent binding and the renal pillary damage associated with PA abusers. (22 refs)

-6292 **Benzo(a)pyrene Metabolism and Plasma Elimination Rates of Phenacetin; Acetanilide and heophylline in Man.** (Eng) Kellermann, G. (Dept. Human ncology, Univ. Wisconsin Medical Sch., Madison, WI); uyten-Kellermann, M. *Pharmacology* 17(4): 191-200; 1978.

he plasma elimination rates of phenacetin (PA), acetanilide AA), and theophylline (TP) were determined in 34 healthy bjects in a search for drugs whose metabolism and regulaon might resemble those of benzo(a)pyrene (BP). The plasa half-lives of PA ranged from 32.0 to 88.2 min, those of A from 70.5 to 186.5 min, and those of TP from 5.1 to 10.4 r. The metabolic clearance rate of PA varied from 11.6 to 74.9 liters/hr, of AA from 7.5 to 18.2 liters/hr, and of TP om 55.8 to 117.0 ml/hr. Statistically significant correlations ere found between (a) the half-lives of PA, AA, and TP and he metabolic clearance rates of AA and TP, and (b) the nducibility of aryl hydrocarbon hydroxylase in mitoen-stimulated lymphocytes; the metabolic clearance rates of A did not correlate. Correlations of the three drugs with he half-lives and metabolic clearance rates of antipyrine (dermined previously) were equally good. In previous studies, ntipyrine metabolism correlated best with BP metabolism. n this study, antipyrine half-lives and metabolic clearance ates were most closely correlated with TP half-lives and clearance rates. The high correlations between antipyrine and PA half-lives contrast with the findings of other studies.(54 refs)

78-6293 **Analgesic Nephropathy and Transitional Cell Carcinoma.** (Eng) Moshakis, V. (Queen Mary's Hosp. for East End, West Ham Lane, Stratford, London E15 4SD, England); Hooper, A. A. *Postgrad Med J* 54(630): 285-286; 1978.

A transitional cell carcinoma of the kidney was found in a 42-yr-old woman who had taken an av of six Codeine compound tablets daily since age 13. This represented a total of 14 kg phenacetin over 26 yr. (4 refs)

78-6294 **Long-Term Safety Evaluation and Metabolism of o-Benzoic Sulfimide (Saccharin) in Rhesus Monkeys.** (Eng) Coulston, F. (Inst. Comparative and Human Toxicology, Albany Medical Coll., Albany, NY, 12208); McChesney, E.; Benitz, K. F. *Ecotoxicol Environ Saf* 2(1): 33-48; 1978.

The results of a 79-mo safety evaluation of saccharin in 7 male and 7 female monkeys are reported. Saccharin was administered by stomach tube 6 days/wk at daily doses of 20 mg/kg (4 animals), 100 mg/kg (4 animals), and 500 mg/kg (6 animals). Six monkeys of comparable age and wt served as controls. Although there were five deaths, one in each treatment group and two in the control group, none of the deaths was related to saccharin intake. The dose regimens had no effect on animal growth or on serum biochemical or whole blood hematological parameters. At necropsy, the only lesions detected grossly or microscopically occurred as frequently in controls as in any of the treated groups. Moreover, the suspected target organ, the urinary bladder, was free of lesions in all groups. Metabolic experiments demonstrated that saccharin was eliminated rapidly (estimated half-life of 9.5 hr), mostly in the urine, and in at least 98% unchanged form. It is concluded that the no-effect level of saccharin for the rhesus monkey exceeds 500 mg/kg/day, a dose that, on a wt basis, is 50 times the recommended max daily human intake. (31 refs)

78-6295 **Effect of DNA Repair Modifying-Factors and Tumor-Promoting Agents on Mutagenesis in a Mammalian Cell Culture System.** (Eng) Lankas, G. R. (Univ. Cincinnati, Cincinnati, OH, 45221). *Diss Abstr Int B* 39(5): 2203-2204; 1978. (no refs)

78-6296 **Aryl Hydrocarbon Hydroxylase Induction in an Insect, *Spodoptera eridania* (Cramer), by Poly-**

chlorinated Biphenyls (PCBs). (Eng) Anderson, R. S. (Donald S. Walker Lab., Sloan-Kettering Inst. Cancer Res., 145 Boston Post Road, Rye, NY, 10580). *Comp Biochem Physiol [C]* 60(1): 51-55; 1978.

Commercial polychlorinated biphenyl (PCB) preparations were tested for their ability to induce aryl hydrocarbon hydroxylase (AHH) activity in terminal instar southern armyworm (*Spodoptera eridania*) midgut homogenates or microsomes. The preparations included Capacitor 21, Aroclor 1016, Aroclor 1242, Aroclor 1254, and several PCB-containing immersion oils. Topical application of PCB's in doses of 2-3 mg induced significant AHH activity, as measured by increased ^{14}C-benzo(a)pyrene substrate metabolism. The induction levels were not proportional to the chlorine content of a given PCB compound. Max induction occurred 24 hr after exposure, and the effect persisted for at least 4 days after a single application of Aroclor 1254. *Spodoptera* homogenate and protein concentrations did not increase within 48 hr of treatment, which suggested that AHH induction by PCB's precedes proliferation of the smooth endoplasmic reticulum. (20 refs)

78-6297 **Effect of Intestinal Microflora on 3,2′-Dimethyl-4-aminobiphenyl-induced Carcinogenesis in F344 Rats.** (Eng) Reddy, B. S. (Naylor Dana Inst. Disease Prevention, American Health Foundation, 1 Dana Rd., Valhalla, NY, 10595); Watanabe, K. *J Natl Cancer Inst* 61(5): 1269-1271; 1978.

The effect of intestinal microflora on colon and breast cancer induced by 3,2′-dimethyl-4-aminobiphenyl (DMAB) was studied in germfree (22 male, 22 female) and conventional (30 male, 30 female) F344 rats. At 7 wk of age, all animals were started on a series of DMAB injections (100 mg/kg/wk x 20, sc). Females were autopsied at 10 wk, males at 15 wk. Tumors were induced in the colons (24/60), duodena (20/60), breasts (24/30 females), ear ducts (9/60), salivary glands (6/60), and skin (36/60) of conventional rats and in the colons (9/44), breasts (9/22 females), ear ducts (6/44), salivary glands (10/44), and skin (4/44) of germfree rats. There was no consistent difference in the incidence of ear duct, salivary gland, and skin tumors between the germfree and conventional rats. However, none of the germfree rats had duodenal tumors, and the incidence of colon and breast cancer was lower in germfree than in conventional rats. In conventional rats, both bacterial and mucosal β-glucuronidase is involved in hydrolyzing the glucuronide conjugate of DMAB, whereas in germfree rats, only mucosal β-glucuronidase is involved. This might explain the difference in colon cancer susceptibility. The possibility that the lower incidence of DMAB-induced colon and breast cancer in germfree rats might be due to their lower hepatic levels of DMAB-metabolizing enzymes cannot be ruled out. (19 refs)

78-6298 **A Sequential Screening of the Cytogenetic Damage Induced by Triaziquone.** (Eng) Oud, J. L. (Inst. Genetics, Univ. Amsterdam, Kruislaan 318, A sterdam, Netherlands); Peters, P. W. *Mutat Res* 54(175-184; 1978.

The suitability of six in vivo cytogenetic tests for determini chromosome damage and the mutagenicity of the alkylati agent triaziquone (TAQ) in young adult random-br Swiss/RIV mice was determined. The mice were inoculat ip either once or twice (24-hr interval) with 0.125 mg/ TAQ. Two injections increased the number of aberratio considerably in both the micronucleus test and the bone ma row metaphase test, but not in the spermatocyte translocati test or the spermatogonial metaphase test. In the latter, strong cell-killing effect of TAQ was noted. Analysis of whc mounts of seminiferous tubules showed that 0.125 mg/kg w a lethal dose for all B- and intermediate-type spermatogor and partly killed A-type spermatogonia. A single dose caus stable chromosome rearrangements in spermatids that cou be demonstrated with the F_1 translocation test, and it ga rise to dominant lethality of fetuses originating from postm otic sperm. The micronucleus test, the results of which a similar to those of the bone marrow test, is concluded to l a reliable and easy screening method for chromosome aberr tions in vivo. The spermatogonial metaphase test can be us to determine the capability of a compound to reach germ cel in seminiferous tubules. The spermatocyte translocation te is informative about stable aberrations in a permanent ce type, and the F_1 translocation and dominant lethal tests r veal the induction of inheritable chromosome rearrangemen in spermatids and spermatozoa. (20 refs)

78-6299 **Carcinogenic Compounds: Synthesis of Polycyclic Carbazole Derivatives by Diels-Alder Reaction.** (Eng) Hiremath, S. P. (Dept. Chemistry, Karnata Univ. Post Graduate Centre, Gulbarga-585 105, India); Kad dargi, S. S.; Purohit, M. G. *J Indian Chem Soc* 55(2 156-157; 1978.

Polycyclic benzocarbazoles were synthesized by Diels-Alde reaction of 3-(β-nitrovinyl)benz(e)indole with various dieno philes such as 1,4-benzoquinone, 1,4-naphthoquinon N-phenylmaleimide, dimethyl acetylenedicarboxylate, an tetracyanoethylene. These compounds are structurally sim lar to polycyclic hydrocarbons, and they have shown carcino genic activity. (13 refs)

78-6300 **The Tumor-producing Effect of Automobile Exhaust Condensate and Fractions Thereof. Part 1: Chemical Studies.** (Eng) Grimmer, G. (Biochemisches In stitut fur Umweltcarcinogene, Sieker Landstrasse 19, 207 Ahrensburg, W. Germany); Bohnke, H. *J Environ Pathol Toxicol* 1(5): 661-667; 1978.

A detection system designed to discriminate between the car cinogenic and noncarcinogenic fractions of a mixture mus

onstrate the following: (1) a reproducible dose/effect re-
n of the carcinogen over a large range; (2) additive effects
o or more carcinogens; and (3) no or negligible influence
rge amounts of ineffective substances on the carcinogenic
t of the carcinogen in a complex mixture. The key for
detection of all carcinogens from a complex mixture and
estimation of their efficiencies is a suitable animal test
em. Automobile exhaust gas condensate was collected
separated into polycyclic aromatic hydrocarbon
H)-containing and PAH-free fractions by liquid-liquid
ribution between methanol + water + cyclohexane and
ohexane + nitromethane, respectively. Carbazol and
dine derivatives as well as aromatic amines remained
lominantly in the PAH-free methanolic phase. Tests in-
ing topical application to the skin of CFLP mice showed
the N-containing and other water-soluble carcinogens do
contribute significantly to carcinogenicity. The results
efore support the assumption that the carcinogenic effect
utomobile exhaust condensate is due to the PAH content.
refs)

6301 **Simultaneous Gas-Chromatographic Profile Analysis of Carcinogenic Polycyclic Aromatic npounds: Polycyclic Aromatic Hydrocarbons, Carbazoles Acridines/Aromatic Amines.** (Eng) Grimmer, G. (Bio-
misches Institut fur Umweltcarcinogene, Sieker Land-
sse 19, 2070 Ahrensburg, W. Germany); Bohnke, H.;
ujack, K. W. *Fresenius Z Anal Chem* 290(2): 147; 1978.

termination of the carcinogenic risk of polycyclic aromatic
npounds to humans by a simultaneous gas-chromato-
phic procedure is outlined. (6 refs)

-6302 **Importance of Inactivating Mechanisms in Chemical Mutagenesis (Meeting Abstract).** ng) Oesch, F. (Section Molecular Pharmacology, Inst.
armacology, Univ., Obere Zahlbacher Strasse 67, D-6500
inz, W. Germany). *Mutat Res* 53(2): 244-245; 1978. (no
s)

-6303 **Apparent and Real Thresholds: A Study on Two Mutagens (Meeting Abstract).** (Eng) Seiler, J.
(Swiss Federal Res. Station, CH-8820 Waedenswil, Swit-
rland). *Mutat Res* 53(2): 260-261; 1978. (no refs)

-6304 **Genetic Activity of Lead Chromate in Bacteria and of Actinomycin D in Yeast (Meeting Ab-
act).** (Eng) Nestmann, E. R. (Environmental Mutagenesis
ction, Dept. Natl. Health and Welfare, Ottawa, Canada).
an J Genet Cytol 20(3): 451; 1978. (1 ref)

78-6305 **Persistent Pesticides and Environmental Chemicals Are Taken Up to a Greater Extent than Non-Persistent Compounds by Cultured Human Cells.** (Eng) Murakami, M. (Inst. Physical Chemical Res., Wako-shi, Saitama 351, Japan); Fukami, J. *Bull Environ Contam Toxicol* 19(4): 423-427; 1978.

Data on the cellular uptake of 11 pesticides by cultured human embryonic lung diploid cells are presented. The pesticides dichlorodiphenyltrichloroethane (DDT), dieldrin, aldrin 2,4,5,2′,5′- hexachlorobiphenyl (PCB), hexachlorobenzene (HCB), carbaryl, malathion, parathion, chlordimeform, 2,4,5- trichlorophenoxy -1- acetic acid (2,4,5-T), and 2,4-dichlorophenoxy-1-acetic acid (2,4-D) showed the following uptake levels (expressed as picomoles/mg cell protein) at 48 hr of incubation: 4,830, 4,380, 3,640, 1,740, 778, 945, 180, 22.6, 32.4, 9.9, and 3.7, respectively. Thus, persistent pesticides such as DDT, dieldrin, aldrin, PCB, and HCB were taken up by cells to a greater extent than nonpersistent pesticides. The considerable amount of carbaryl taken up by the cells suggests that the naphthalene ring in the carbaryl molecule may be involved in the incorporation potential of this compound. The effect of the above pesticides on cell growth was also investigated; most compounds were not toxic at the same concentration (4×10^{-6} M) and over the same experimental period as in the uptake experiments. The herbicides 2,4-D and 2,4,5-T, although less incorporated than the insecticidal and industrial chemicals, appeared to be more toxic. It is evident that differences in uptake are not the cause of the different degrees of cytotoxicity of the chemicals. (13 refs)

78-6306 **Tumor-promoting Phorbol Esters Inhibit Binding of Epidermal Growth Factor to Cellular Receptors.** (Eng) Lee, L. S. (Inst. Cancer Res., Coll. Physicians and Surgeons, Columbia Univ., New York, NY, 10032); Weinstein, I. B. *Science* 202(4365): 313-315; 1978.

Tumor-promoting phorbol esters and related plant diterpenes were tested for their ability to inhibit the binding of ^{125}I-labeled epidermal growth factor (EGF) to HeLa cells. Extremely low concentrations [0.25-50 nanograms (ng)/ml] of 12-O-tetradecanoylphorbol-13-acetate (TPA) and related compounds produced a dose-dependent decrease in ^{125}I-EGF binding. At 25 ng/ml (4.2×10^{-8} M), TPA inhibited the binding of ^{125}I-EGF by 90%. In decreasing order of effectiveness, the test compounds that inhibited EGF binding were TPA, merzerein, gnilatimacrin, gnidilatin, phorbol -12,13-didecanoate (PDD), and phorbol dibenzoate. Inhibition occurred when the test agent was added 90 min before or simultaneously with EGF. Phorbol, 4α-phorbol-12,13-didecanoate, 4-O-methyl-12-O-tetradecanoylphorbol-13-acetate, gnidipalmin, and anthralin did not have an appreciable effect on ^{125}I-EGF binding when tested at concentratons up to 100 ng/ml. The inhibitory effect, therefore, occurs at concentrations as low as 10^{-8}-10^{-9} M and possesses marked structural specificity and stereospecificity. These re-

sults also parallel the structural requirements for promoting activity in the two-stage mouse skin carcinogenesis assay. Inhibition of binding appears to be due to a decrease in the number of available EGF receptors rather than to a change in receptor affinity. These results suggest that certain biologic effects of tumor promoters may result from alterations in the function of cell-surface receptors involved in growth regulation. (48 refs)

78-6307 **Blocking Tumor Promotion by Protease Inhibitors.** (Eng) Troll, W. (Dept. Environmental Medicine, New York Univ. Medical Center, New York, NY, 10016); Levitz, M. *In: Prevention and Detection of Cancer. Proceedings of the Third International Symposium on Detection and Prevention of Cancer Held by the International Study Group for the Detection and Prevention of Cancer in New York, April 26 - May 1, 1976.* International Study Group for the Detection and Prevention of Cancer. (New York, NY): Vol. 2(Part 1), 2404 pp.; 1245-1250; 1978.

The influence of protease inhibitors on tumor promotion in mouse skin and the association between estrogens and plasminogen activation in mouse uterus were investigated. Treatment of mouse skin with 1 μg phorbol myristate acetate (PMA) resulted in the appearance of appreciable protease activity (35 fluorescence units/mg protein/hr); this activity was inhibited by tosyllysine chloromethyl ketone, a protease inhibitor. In skin tumor studies, tumor appearance was delayed 50-100 days by the application of protease inhibitors 3x/wk. Tumors initiated on the skin of female mice with 7,12-dimethylbenz(a)anthracene and promoted 2 wk later with croton oil were suppressed by the application of glucocorticoids (dexamethasone, Schering No. 11572, prednisolone, hydrocortisone, and cortisone) at 6 and 30 μg, 5x/wk. Tissue culture studies indicated that dexamethasone elaborates a protease inhibitor. The association between estrogens and plasminogen activation was investigated by treating ovariectomized young mice with 0.1 μg estradiol bid for 3 days. This resulted in the appearance of plasminogen activator specifically localized in the 12,000 *g* pellet, perhaps bound to the plasma membrane, and the nucleus. Inoculation of normal cycling female mice with a mixture of the protease inhibitors Antipain (3.0 mg) and Leupeptin (20 mg) for 15 days caused a significant diminution in uterine wt, total DNA, and total protein. The role of plasminogen activator may be at an early stage of tumor promotion; hormones may act in a similar manner. (12 refs)

78-6308 **The Nucleotide-Permeable *Escherichia coli* Cell, a Sensitive DNA Repair Indicator for Carcinogens, Mutagens, and Antitumor Agents Binding Covalently to DNA.** (Eng) Thielmann, H. W. (Deutsches Krebsforschungszentrum, Institut fur Biochemie, Im Neuenheimer Feld 280, D-6900 Heidelberg, West Germany); Gersbach, H. *Z Krebsforsch* 92(2): 177-214; 1978.

The use of ether-permeabilized (nucleotide-permeable) *cherichia coli* cells in assay of capability for DNA-binc and stimulation of excision repair of 11 ultimate carcinog 10 proximate carcinogens, 2 tumor promotors, 6 mutag and 12 antitumor agents was investigated. The strains o *coli* used in the study were the wild types, H 540, KMBL 1 $polA_{107}$, and KMBL 1789, and the mutants *uvr* A(H 512) *uvr* B(H 551). All the ultimate carcinogens (alkylating, a lating, arylalkylating agents) and the mutagens such as drogen peroxide and acridine derivatives caused DNA e sion repair in wild type cells and simultaneously inhib replication DNA synthesis to various degrees. Proximate c cinogens such as dimethyl nitrosamine and the aflatoxins t require activation for DNA-binding did not induce excis repair. Intercalating mutagens such as quinacrine and eth um bromide inhibited replicative DNA synthesis, howe they were not repair inducers. The tumor promot 12 -O- tetradecanoyl-phorbol -13- and phorbol -12, didecanoate did not cause excision repair, even wh applied in high concentrations, nor did they inh repair synthesis stimulated by N-methyl -N- nitrosou or N-acetoxy-2-acetylaminofluorene. The antitun agents were classified in two groups on the basis of th effect on DNA synthesis: members of the first gro known to bind covalently to DNA [bleomycin, N, bis(2-chloroethyl) -N- nitrosourea, etc] stimulated pair polymerization and inhibited DNA replicati the other group of antitumor agents, known to re with DNA by noncovalent binding [*cis*-Pt(II) diam complexes, adriamycin, etc] inhibited DNA replicati without stimulating repair synthesis. It is conclud that the ether-permeabilized *E. coli* cell can be succe fully used as assay for DNA repair-inducing and repli tion-inhibiting activity. (110 refs)

78-6309 **Effect of Tumor Promoters on the Response Cultured Embryonic Chick Ganglia to Ner Growth Factor.** (Eng) Ishii, D. N. (Dept. Pharmacolog Coll. Physicians and Surgeons, Columbia Univ., New Yor NY, 10032). *Cancer Res* 38(11, part 1): 3886-3893; 1978.

The effects of the tumor-promoting agent 12-O-tetradeca oylphorbol-13-acetate (TPA) on nerve growth fact (NGF)-induced neurite outgrowth (NOG) were studied cultured chick embryonic ganglia. There was no detectab NOG in the absence of NGF, but in its presence [1 nan gram(ng)/ml], a max response was attained in 24 hr and su tained for at least 48 hr. The addition of TPA (100 ng/m 1.7×10^{-7} M) to the culture medium inhibited further NO for 24 hr, after which there was a gradual increase in ou growth, even in the presence of fresh TPA. Neurites forme in the presence of NGF (10 ng/ml) + TPA (200 ng/ml) wer shorter, thicker, and sparser than those of NGF-treated cu tures. In cytotoxicity tests, TPA alone substantially enhance the survival of ganglion cells. TPA + NGF appeared to in crease the number of surviving cells over that produced wit either agent alone. Thus, TPA is not cytotoxic to ganglio cells at concentrations that antagonize NGF. Other plant di

enes that are tumor promoters in the mouse skin carcinoesis system (phorbol-12,13-didecanoate, ingenol dibenzo- and mezereine) also inhibited the ganglia response to F, but structurally ralated nonpromoting compounds e inactive. The concentration of NGF that induced a f-max NOG response in sensory ganglia was 0.6 x 10^{-11} The antagonism of NGF by TPA was dose-dependent noncompetitive. TPA concentrations that extensively inited NOG did not affect the amount of ^{125}I-labeled NGF nd to specific sites on dissociated dorsal root ganglion s, supporting the theory that TPA acts at a stage beyond initial interaction of the factor with its receptive site. (51 s)

6310 **Specificity of Response in Hamster Cells Induced to Produce Plasminogen Activator by the mor Promoter, 12-O-Tetradecanoylphorbol-13-acetate.** ng) Christman, J. K. (Dept. Biochemistry, Mount Sinai edical Center, New York, NY, 10029); Copp, R. P.; Pedri-i, L.; Whalen, C. E. *Cancer Res* 38(11, part 1): 3854-3860; 78.

e effect of the tumor-promoting agent 12-O-tetradecanoylorbol-13-acetate (TPA) on the form of plasminogen activa- (PA) produced by cells in culture was studied using severhamster cell lines. TPA enhanced PA production only in mster cells that synthesize a PA that is immunologically ntical to that of normal hamster lung cells. No enhancent of PA production was detected in hamster cells (kidys, ovary, melanoma, or glioma) that synthesize a PA of ferent antigenic form. Neither the tissue of origin nor the nsforming agent served as an absolute determinant of the rm of PA produced. Two of three simian virus 40 V40)-transformed early-passage Chinese hamster lung es, a subclone of the DON hamster lung line selected for azaguanine resistance, and one of two SV40-transformed mster kidney lines produced the lung-type PA. Cells of the ird SV40-transformed lung culture produced a PA distinct om that of normal hamster lung cells. In the presence of PA, however, this line synthesized PA of the lung form. hus, TPA was able to induce the reexpression of at least one rameter of the original phenotype, synthesis of the lung rm of PA. These results suggest that the two antigenically stinct PA's are separate gene products. The relationship, any, between the ability of TPA to increase PA production nd its ability to promote tumor formation in mouse skin is ot known. (46 refs)

8-6311 **Distribution of 3-Hydroxyanthranilic Acid in Mice.** (Eng) Watanabe, M. (Dept. Analytical hemistry, Faculty Pharmaceutical Sciences, Teikyo Univ., agamiko, Kanagawa-ken 199-01, Japan). *Gann* 69(4): 85-587; 1978.

Male (BALB/c x DBA/2)F_1 mice were inoculated sc with ^{3}H-hydroxyanthranilic acid (^{3}H-HAA: 2 mg, 748 μCi) and, 30 and 60 min and 6 hr later, the distribution of ^{3}H was observed by whole-body autoradiography and radioactivity measurements, and metabolites in organs and urine were measured by paper and thin-layer chromatography. At 30 and 60 min after injection, the radioactivity was found mainly in the liver and kidneys; it was distributed almost uniformly in other organs. After 6 hr, the radioactivity remained in the kidneys and lymphoid organs. However, at 30 min and 6 hr after injection, neither HAA nor any carcinogenic metabolites could be detected in the liver, kidneys, spleen, or lymph nodes. Considerable amounts of HAA and its sulfate were found only in urine. These results suggest that HAA is metabolized rapidly and does not accumulate in a specific organ. However, urinary organs may be at risk of tumor development because of the rapid excretion of most of the compound in urine. (8 refs)

78-6312 **Studies on the Hepatic Microsomal Metabolism of [^{14}C]Phenanthrene.** (Eng) Chaturapit, S. (Dept. Pharmacy, Univ. Sydney, New South Wales 2006, Australia); Holder, G. M. *Biochem Pharmacol* 27(14): 1865-1871; 1978.

The metabolism of ^{14}C-phenanthrene by liver microsomes from Wistar rats, SW and DBA/2J mice, and guinea pigs was examined using untreated, sodium phenobarbital (PB)-pretreated, and 3-methylcholanthrene (3-MC)-pretreated animals. Metabolite profiles were obtained by comparing the thin-layer chromatographs of the reaction products with chromatographs of authentic reference compounds. Trans-Dihydrodihydroxyphenanthrenes were the major metabolites in all preparations. With all reactions except for the one in which microsomes from 3-MC-pretreated guinea pigs were used, trans-9,10-dihydro-9,10-dihydroxyphenanthrene predominated. With microsomes from the 3-MC-pretreated guinea pigs, phenanthrene 1,2-dihydrodiol was the major metabolite. Addition of cyclohexene oxide (5.0 mM) to the incubation mixture inhibited dihydrodiol formation in rat and mouse preparations by 90% and in guinea pig preparations by 70%. Phenols and phenanthrene 9,10-oxide were produced instead. Compared with control microsomes, increases in phenanthrene metabolism occurred with microsomes from all PB-pretreated animals and with microsomes from 3-MC-pretreated rats and SW mice, a pattern similar to that seen for the induction of aryl hydrocarbon hydroxylase. (43 refs)

78-6313 **Excision of Hydrocarbon-DNA Adducts and Consequent Cell Survival in Normal and Repair Defective Human Cells.** (Eng) McCaw, B. A. (Chemical Carcinogenesis Program, NCI Frederick Cancer Res. Center, Frederick, MD, 21501); Dipple, A.; Young, S.; Roberts, J. J. *Chem Biol Interact* 22(2/3): 139-151; 1978.

An attempt was made to demonstrate selectivity of excision in normal human fibroblasts, xeroderma pigmentosum (XP) variants that are not deficient in excision repair, and in partially excision-repair-deficient XP fibroblasts. Survival curves for UV-irradiated normal human cells and XP variant cells (XPB4BE) were indistinguishable. In comparison, cells from XP complementation group A (XP12BE) were very sensitive to UV radiation. Complementation group C (XP2BE) cells were almost as sensitive as group A cells. These survival phenomena paralleled the known unscheduled DNA synthesis responses of these cells to UV radiation, which, compared with normal cells, are: XP4BE, 100%; XP2BE, 20%; XP12BE, 2%. The relative capacities of these cells to excise 7-bromomethylbenz(a)anthracene (BMBA)-DNA adducts and to survive treatment with the carcinogen were similar to the responses to UV radiation, except that the XP2BE cell line excised and survived this damage far better than anticipated from its response to UV radiation. Moreover, although the ratio of hydrocarbon-adenine adduct to hydrocarbon-guanine adduct remaining in DNA decreased notably with excision in normal and variant cells, this ratio did not change significantly with excision in XP2BE cells. The relationship between greater excision capacity and increased cell survival in the experiments with BMBA indicates that the unexcised damage is responsible for the cell-killing action of this agent. The different relative repair and survival responses of these cell lines to UV radiation and to BMBA indicate that in at least one of these cell lines (XP2BE), and possibly all the lines, different cellular mechanisms are involved in the repair of DNA damage resulting from UV radiation and that resulting from chemical carcinogen treatment. (22 refs)

78-6314 **Cytogenetic Mapping of the Trisomic Segment of Chromosome 15 in Murine T-Cell Leukemia.** (Eng) Wiener, F. (Dept. Tumor Biology, Weizmann Inst. Science, Rehovot, Israel); Ohno, S.; Spira, J.; Haran-Ghera, N.; Klein, G. *Nature* 275(5681): 658-660; 1978.

A chromosome segment located distal to the T6 breakpoint of chromosome 15 was found to be duplicated in 7,12-dimethylbenz(a)anthracene-induced T-cell leukemia in CBAT6T6 mice. These leukemias are associated with trisomy 15, a nonrandom cytogenetic change also associated with murine T-cell leukemia induced by viruses and x-rays. The induced leukemias were transplanted sc into recipient mice of the opposite sex, and G-banded metaphase plates were prepared from sc tumors, spleens, and bone marrow. Five of six leukemias were aneuploid, with 41 or 42 chromosomes. All the aneuploid leukemias had a trisomy T(14:15)6. The sixth tumor, however, had a banding pattern indistinguishable from that of a normal CBAT6T6 cell. The consistency of the trisomic change emphasizes the specific role of genes associated with chromosome 15 in T-cell leukemia. However, the occurrence of a diploid leukemia in one tumor shows that the change is not exclusive. (9 refs)

78-6315 **Chemical Carcinogenesis in C3H/StWi M a Worthwhile Experimental Model for Bre Cancer.** (Eng) Smith, G. H. (Lab. Molecular Biology, N Bethesda, MD, 20014); Pauley, R. J.; Socher, S. H.; Medi D. *Cancer Res* 38(12): 4504-4509; 1978.

To determine whether the low incidence of mammary tum in C3H/StWi mice is due to the fact that low-oncoge mouse mammary tumor virus MMTV(L) is not expressed these mice, the effects of estrogenic stimulation and 7,12-dimethylbenz(a)anthracene (DMBA) on mammary mor incidence were examined in C3H/StWi and (BALB/c x C3H/StWi)F_1 mice. None of 18 virgin C3H/StWi fema in which 20% diethylstilbestrol (DES) pellets were implant sc at 5-6 wk of age developed mammary cancer throughc their life-span, which averaged 24.5 mo. Only 2/24 hyb mice similarly treated developed mammary cancer. In co trast, 17/37 virgin C3H/StWi mice treated with DMBA mg/wk, intragastrically) over a 6-wk period developed ma mary tumors at an av age of 7.8 mo (range, 4.5-10 mo). T tumors were mainly papillary adenocarcinomas. Mamma dysplasias were found in 73% of the whole-gland mou examined at 10 mo (3.6 mouse). All but three dysplasias w ductal in origin. No hyperplastic alveolar nodules w found. Electron microscopic examination of 14 DMBA- duced mammary tumors failed to reveal the presence of or B-type particles, but 11 tumors contained budding a extracellular C-type virions. Evaluation of five tumors MMTV-specific RNA sequences indicated levels as low or lower than those found in the mammary glands of c retired multiparous C3H/StWi females (0.0035%). Mu higher levels (0.2%-0.4%) of MMTV-specific RNA to to RNA occurred in MMTV-induced C3H/StWi mammary t mors. Thus, the C3H/StWi subline is different from oth C3H sublines in view of its low mammary cancer incidenc low response to estrogenic stimulation, and the fact that does not produce MMTV(L). It may represent a unique mo el for the study of viral, chemical, and viral-chemical intera tions in the malignant transformation of mammary epitheli cells. (21 refs)

78-6316 **A Technique for Localization of Tumours Hamster Cheek-Pouch Carcinogenesis.** (En MacDonald, D. G. (Dept. Oral Medicine and Patholog Glasgow Dental Hosp. and Sch., 211 Renfew St., Glasgo G2 3JZ, Scotland). *Arch Oral Biol* 23(7): 573-577; 1978.

A technique was developed to enable the area of exposure a carcinogen and of subsequent tumor growth to be predete mined and restricted in the hamster cheek pouch. Thirty ma Syrian hamsters received either 0.5% or 0.25% 9,10-dimeth yl-1,2-benzanthracene (DMBA) topically, 3x/wk for 6 w in a restricted (1-cm^2) anterior portion of both cheek pouche just posterior to the prominent blood vessels at the pouc mouth. At 15 wk posttreatment, all animals were sacrifice and examined surgically. Tumors were first evident at 5 w posttreatment, and by time of biopsy at 8 wk, 11 animals ha

ors in 13 pouches, but there was no significant difference veen the two treatment groups with respect to tumor yield listribution. At sacrifice, 19 animals had developed tu- s in 30 pouches, many at multiple sites. In 13 pouches, tumors were within the experimental area; in 9, they were ide this area; and in 8, tumors were within and without defined area. Again, there was no significant difference veen the two treatment groups with respect to tumor yield listribution, but the 0.25% group showed significantly er tumor localization in terms of pouches with tumors de the experimental area only (8/9 pouches) compared n pouches with tumors outside this area only. This means ocalization allows sequential studies of carcinogenesis in efined area to be undertaken. (7 refs)

6317 **Azo Dyes Prevent Hydrocarbon-induced Leukemia in the Rat.** (Eng) Huggins, C. B. (Ben y Lab. Cancer Res., Univ. Chicago, Chicago, IL, 60637); la, N.; Russo, A. *Proc Natl Acad Sci USA* 75(9): 4-4527; 1978.

e azo dyes 1-(p-phenylazophenylazo)-2-naphthol (Sudan and 1-(o-tolylazo-o-tolylazo)-2-naphthol (Sudan IV) e investigated as possible protectors against leukemia in- ed by multiple injections of 7,8,12-trimethylbenz(a)an- acene (7,8,12-TMBA) in Long-Evans rats. Three groups female rats were given four 35-mg/kg injections of 12-TMBA, iv, 2-wk intervals. Two groups were fed 1 mg ither dye 24 hr before each iv injection; controls were fed me oil. In rats fed Sudan III, leukemia incidence was %, mammary cancer incidence 60%. Analogous figures rats fed Sudan IV were 21% and 57%. Of control rats, % developed leukemia and 43%, mammary cancer. Three ups of male rats received 7,8,12-TMBA as above. Two ups received Sudan III at 48 and 24 hr prior to each ction, one (Group I) at a dose of 1 mg, and the other oup II) at a dose of 10 mg. The incidence of leukemia in oup I was 6%, that in Group II, 0%. Controls developed kemia at a rate of 92%. Daily feeding of 1 mg Sudan III ight female rats for 4 days produced a progressive increase he hepatic menadione reductase concentration, but the tein concentration was unchanged. A single iv injection 5 mg/kg 7,8,12-TMBA produced a transient leukopenia, no changes in WBC counts were seen in similarly treated s protected with 1 mg Sudan III. All 16 female rats given ingle injection of 75 mg/kg 7,12-DMBA expired in 1-3 s. In an identical group protected with 1 mg Sudan III hr before DMBA injection, no rats died, although 50% ntually developed leukemia. Sudan III itself was not found be carcinogenic. (18 refs)

-6318 **Development of Experimental Brain Tumors under Amine Metabolism Modulation.** (Rus) umanis, E. A. (Dept. Pharmaceutical Chemistry, Riga Medical Inst., Riga, USSR); Plaude, O. O.; Buikis, I. M. *Vopr Onkol* 24(9): 71-77; 1978.

9,10-Dimethyl-1,2-benzanthracene (DMBA)-induced brain tumor mortality and its relationship to brain serotonin levels were studied over a 10-mo period in Wistar rats wth DMBA implanted into their cerebellum. The development of cerebellar tumors was accompanied by a depletion of the serotonin level in the cerebellum, but the level in the hypothalamus remained unchanged. An inverse correlation was found between DMBA-induced brain tumor mortality and serotonin levels. Topical administration of monoamine oxidase inhibitors before the precancerous stage (before day 120 after DMBA implantation) reduced tumor incidence and tumor mortality by reducing the number of astrocytomas and histogenetically related glioblastomas. The monoamine oxidase inhibitors had no effect on the malignant transformation of other neuroectodermal cells. The findings indicate that serotonin (the levels of which are increased by monoamine oxidase inhibitors) increases the resistance of astrocytes to malignant transformation. (21 refs)

78-6319 **Hemopexin and Aryl Hydrocarbon Hydroxylase Induction in the Mouse and in Cell Culture.** (Eng) Owens, I. S. (Developmental Pharmacology Branch, Natl. Inst. Child Health and Human Development, NIH, Bethesda, MD, 20014); Nebert, D. W.; Liem, H. H.; Muller-Eberhard, U. *Biochem Pharmacol* 27(12): 1665-1669; 1978.

Hemopexin (HP) and aryl hydrocarbon hydroxylase (AHH) induction among inbred mouse strains and among offspring derived from appropriate genetic crosses was examined along with HP and AHH levels in several rat hepatoma-derived cell culture lines to determine whether an association exists between HP induction and the Ah allele. Treatment of three responsive mouse strains, C57BL/6N (B6), Balb/cAnN, and C3H/HeN, with a single dose (80 mg/kg, ip) of 3-methylcholanthrene (3-MC) or β-naphthoflavone (NF) increased plasma HP levels 71%-160%. The nonresponsive strains DBA/2N, NZB/BLN, and NZW/BLN had increases of 14% to 60%. In B6 mice, the greatest rise in HP levels occurred between 24 and 48 hr. AHH activity induced by 3-MC occurred during the first 24 hr. The increase in HP therefore appears to be subsequent to AHH induction by 3-MC. Administration to the mice of 0.05% phenobarbital in drinking water for up to 14 days induced similar levels of AHH activity in both responsive and nonresponsive mice. Again, the increase in HP followed AHH induction. AHH was not inducible in 6/18 3-MC treated (B6 x NZW)F_2 offspring. In hepatoma cell lines grown in culture and treated with 13 μM benz(a)anthracene (BA), HP production occurred in H-4-II-E but not in HTC or Hepa-1 cells, but a relationship between inducible AHH activity and plasma HP levels could not be inferred. HP appearance was equivalent in BA-treated and control H-4-II-E cultures, whereas AHH induction occurred primarily in the BA-treated cultures. Frequent remov-

al of tissue culture medium resulted in an increased secretion of intracellular HP to the surrounding medium. The reason for this effect is not known. (33 refs)

78-6320 **The Topology of Epoxide Hydratase and Benzpyrene Monooxygenase in the Endoplasmic Reticulum of Rat Liver.** (Eng) Seidegard, J. (Arrhenius Lab., Dept. Biochemistry, Univ. Stockholm, Fack, S-106 91 Stockholm, Sweden); Moron, M. S.; Eriksson, L. C.; DePierre, J. W. *Biochim Biophys Acta* 543(1): 29-40; 1978.

The distribution of benzo(a)pyrene monooxygenase and epoxide hydratase, in the liver microsome subfractions of control and of phenobarbital (PB)- and methylcholanthrene(MC)-treated rats was investigated. Male Sprague-Dawley rats were injected ip with 20 mg/kg MC on days 5, 3, and 1 before sacrifice or with 80 mg/kg PB on days 5-1 before sacrifice. The specific activities of these enzymes in the rough and smooth microsomes from control and PB-treated rats were approx equal. After treatment with MC, however, the activity of benzo(a)pyrene monooxygenase was four times higher and that of epoxide hydratase two times higher in the rough vesicles. Differential centrifugation revealed that both enzymes were dispersed uniformly throughout the microsomal vesicles. It is concluded that these two enzyme systems may form a complex of unique stoichiometry in the microsomal membranes from control rats, not in those from MC-treated rats. Studies with proteases and diazobenzene sulfonate suggest that epoxide hydratase is located deep within the lipid phase of the membrane of the hepatic endoplasmic reticulum. (31 refs)

78-6321 **An Experimental Approach to the Breast Cancer, Reserpine Problem.** (Eng) Homburger, F. (Bio-Res. Inst., 9 Commercial Ave., Cambridge, MA, 02141); Van Dongen, C. G.; Adams, R. A.; Soto, E. A.; Pai, K. J. *Cancer Lett* 4(3): 177-183; 1978.

The effect of reserpine on methylcholanthrene (MC)-induced breast cancer was studied in BIO 15.16 Syrian hamsters, a strain previously shown to be sensitive to the induction of mammary cancer by MC. There were seven experimental groups. Group 0 (25 hamsters) received 10 μg reserpine ip three times weekly for life. (An initial dose of 100 μg was reduced after 1 wk because of intolerance.) Group I (25) received 50 gastric gavages of 0.05 mg MC. Group II received (25) reserpine + MC. Group III received reserpine + 50 gavages of 0.1 mg MC. Group IV received 50 gastric gavages of 4 mg MC. Group V received the vehicle for reserpine and MC. Group VI received no treatment. All MC doses except the 4-mg dose were noncarcinogenic. The survival curves of all groups except Group IV were not significantly different from each other. Mammary tumors were noted only in 11 Group IV animals; other Group IV tumors included 3 adenocarcinomas of the colon and cecum, 2 lymphomas, and 2 sarcomas. Multiple mammary tumors were a frequent find Metastasis of mammary gland carcinoma to the cervical, a lary, and/or inguinal lymph nodes was observed in 10 mals, metastases to the lungs in 2. No tumors were note Groups 0 and I. Group II had 1 sarcoma, Group III 2 l phomas, Group V 1 sarcoma, and Group VI 1 lympho The results do not conclusively rule out or demonstrate cocarcinogenicity of reserpine. (9 refs)

78-6322 **Metabolic and Enzymatic Factors in Tu Susceptibility.** (Eng) Kellermann, G. H. (D Human Oncology, Univ. Wisconsin Medical Sch., Madis WI). *In: Prevention and Detection of Cancer. Proceeding the Third International Symposium on Detection and Pre tion of Cancer Held by the International Study Group for Detection and Prevention of Cancer in New York, April May 1, 1976.* International Study Group for the Detect and Prevention of Cancer. (New York, NY) : Vol. 2 (I I), 2404 pp.; 1517-1524; 1978.

The relationship between aryl hydrocarbon hydroxyl (AHH) activity and susceptibility to carcinogenic polycy aromatic hydrocarbons (PAH) was studied. Human ly phocytes were cultured for 2 days in the presence of 2 m gens (phytohemagglutinin and pokeweed) prior to the ministration of 3-methylcholanthrene or benzanthracene induce AHH activity. Individual inducibility was expres as the ratio of AHH activity in the PAH-treated cultures AHH activity in the cultures without treatment. The ly phocytes were obtained from 289 normal subjects, patie with bronchogenic carcinoma (50) or laryngeal carcinor (37), and 46 patients (cancer control group) with Hodgki disease or cancers of the skin, gastrointestinal tract, head a neck, breast, uterus, prostate or bladder. Previous family a population studies have revealed considerable interindivid variation of this enzyme complex and demonstrated its ger ic control. Ninety percent of the healthy subjects had low intermediate AHH inducibilities in their lymphocytes. Ho ever, 96% of the lung cancer patients, all heavy smokers, h intermediate (66.0%) or high (30.0%) AHH inducibiliti This distribution pattern was not seen in the laryngeal can patients (19.0% with high inducibility) or in the cancer co trol group (10.9% with higher inducibility). It is suggest that cigarette smokers with high AHH inducibility have higher risk of developing lung cancer than persons with l inducibility. Ninety percent of the 289 healthy subjects h low (114) or intermediate (118) AHH inducibilities in th lymphocytes. (18 refs)

78-6323 **1,2-Dihydro-1,2-dihydroxy-5-methylchrysene A Major Activated Metabolite of the Enviro mental Carcinogen 5-Methylchrysene.** (Eng) Hecht, S. (Div. Environmental Carcinogenesis, Naylor Dana Inst. D ease Prevention, American Health Foundation, Valhal

, 10595); LaVoie, E.; Mazzarese, R.; Amin, S.; Bedenko, Hoffmann, D. *Cancer Res* 38(7): 2191-2194; 1978.

e metabolic activation of the environmental carcinogen ethylchrysene was studied by combining high-pressure id chromatographic analysis of metabolites formed in vi- with assays of these metabolites for mutagenic activity ard *Salmonella typhimurium*. Metabolites were formed the incubation of 5-methylchrysene with the 9000 x *g* ernatant from Aroclor-treated rat livers. With the use everse-phase columns, the metabolites were resolved into e peaks. Significant mutagenic activity was observed narily in one peak and to a lesser extent in a second peak. e major mutagenic metabolite was identified as 1,2-dihy--1,2-dihydroxy-5-methylchrysene (7.0% from 5-methyl-ysene), and the secondary mutagenic metabolite was iden-d as 7,8-dihydro-7,8-dihydroxy-5-methylchrysene (2.6% n 5-methylchrysene). The results indicate that 1,2-dihy--1,2-dihydroxy-5-methylchrysene is a proximate mutagen -methylchrysene and support the hypothesis that carcino-ic polynuclear aromatic hydrocarbons can be activated ough the formation of specific angular ring diol-epoxides. refs)

6324 **Relationship Between DNA Damage, Cell Survival and DNA Repair in CHO Cells after In ro Metabolic Activation of Promutagens (Meeting Abct).** (Eng) Douglas, G. R. (Environmental Mutagenesis tion, Dept. Natl. Health and Welfare, Tunney's Pasture, awa, Canada); Grant, C. E. *Can J Genet Cytol* 20(3): 442; 8. (no refs)

-6325 **Carcinogen-induced DNA Repair in Nucleotide-Permeable *Escherichia coli* Cells. Analysis DNA Repair Induced by Carcinogenic K-Region Epoxides 1,2,3,4-Diepoxybutane.** (Eng) Thielmann, H. W. (Deutes Krebsforschungszentrum, Institut fur Biochemie, Im uenheimer Feld 280, D-6900 Heidelberg, West Germany); rsbach, H. *Z Krebsforsch* 92(2): 157-176; 1978.

zymic activities catalyzing DNA repair in ether-perabilized (nucleotide-permeable) *Escherichia coli* cells exed to carcinogenic K-region epoxides or the aliphatic oxide 1,2,3,4-diepoxybutane (DPB) were identified by ermination of repair polymerization and size reduction of natured DNA. The requirement for the *uvr* gene function excision repair was tested using wild type and *uvr* A and B mutant *E. coli* cells. When exposed to the carcinogenic region epoxides 7-methyl- and 7,12-dimethylbenz(a)anacene-5,6-oxide, chrysene-5,6-oxide, and benzo(a)pye-4,5-oxide, the wild type cells (KMBL 1788; H 540) exited DNA excision repair, but the *uvr* A and *uvr* B cells not. The K-region epoxide phenanthrene-9,10-oxide was ffective in all *E. coli* strains tested. DPB and the 6,7-epoxs of the tumor promotor, 12-O-tetradecanoyl-phorbol-13-acetate, elicited DNA repair in the *uvr* A and *uvr* B mutant cells. None of the epoxides induced repair polymerization in a mutant that lacked the 5′-3′ exonucleolytic activity of DNA polymerase I (exonuclease VI). Greatly reduced levels of repair polymerization were observed in mutants that lacked DNA polymerase I. It is concluded that excision of K-region epoxide damaged nucleotides is controlled, at least in part, by three repair enzyme activities: a UV-endonuclease (missing in the *uvr* mutants), the 5′-3′ exonucleolytic activity of DNA polymerase I, and an intact DNA polymerase. Excision of DPB damaged nucleotides requires in addition a *uvr*-independent repair endonuclease, which is probably endonuclease II, DNA glycosidase(s), and/or apurinic endonuclease(s). (58 refs)

78-6326 **Studies on the Metabolic Activation of Benzo(a)pyrene and Subsequent Binding to Nuclear Macromolecules.** (Eng) Pezzuto, J. M. (Coll. Medicine and Dentistry, New Jersey Graduate Sch. Biomedical Sciences, Newark, NJ, 07103). *Diss Abstr Int B* 39(5): 2281-2282; 1978. (no refs)

78-6327 **Benzo(a)pyrene Absorption from the Intestinal Tract of the Rat with Emphasis on Lymphatic Uptake and Tissue Distribution.** (Eng) Reid, J. B. (Univ. Cincinnati, Cincinnati, OH). *Diss Abstr Int B* 39(5): 2205; 1978. (no refs)

78-6328 **Antimutagenic Effects of 2(3)-*tert*-Butyl-4-hydroxyanisole and of Antimicrobial Agents.** (Eng) Batzinger, R. P. (Dept. Pathobiology, John Hopkins Medical Inst., Baltimore, MD, 21205); Ou, S. Y.; Bueding, E. *Cancer Res* 38(12): 4478-4485; 1978.

To determine antimutagenic effects of the antioxidants 2(3)-*tert*-butyl-4-hydroxyanisole (BHA) and ethoxyquin (EQ), diets containing 0.75% BHA or 0.5% EQ were fed to female CD-1 mice that were subsequently treated with benzo(a)pyrene (BP: 100 mg/kg im in sesame oil), hycanthone (60 mg/kg im as the aqueous soln of methane sulfonate salt), and metronidazole, diazepam, or membendazole (each 200 mg/kg by gastric intubation). BHA and EQ markedly decreased the level of mutagens present in BP-treated mice, as determined by a host-mediated assay and tests with *Salmonella typhimurium* strains TA100 and TA98. BHA also reduced the mutagenic activities in vivo of the four antischistosomal compounds. These effects were accompanied by increases in the thiol levels of some tissues. The production of mutagenic metabolites of two other antischistosomal drugs, 4-isothiocyano-4′-nitrodiphenylamine and oxamniquine, was not reduced by BHA treatment. However, reductions in mutagenicity were achieved by the administration of enteric antibacterial agents, which implicates intestinal microorgan-

isms in the mutagenic activation of certain chemical agents. Combined treatment of mice with BHA and enteric antimicrobial agents reduced the levels of mutagens derived from metronidazole by more than 90%, and the combined treatments were more effective than was either treatment alone. (37 refs)

78-6329 **Selective Fluorescence Quenching of Benzo(a)pyrene and a Mutagenic Diol Epoxide Derivative in Mouse Cells.** (Eng) Wade, C. G. (Dept. Chemistry, Univ. Texas at Austin, Austin, TX, 78712); Baker, D. E.; Bartholomew, J. C. *Biochemistry* 17(20): 4332-4337; 1978.

Fluorescence and flow cytometric studies were made of the effects of various quenchers on suspensions of cultured mouse cells containing benzo(a)pyrene (BP) and its diol expoxide (DE) 7β, 8α-dihydroxy-9α, 10α-epoxy-7,8,9,10-tetrahydrobenzo(a)pyrene The overlap of the fluorescence spectra of BP and its metabolites, particularly the DE, had previously prevented the use of fluorescence in investigations of the impact of these carcinogens on cell populations. The cells used were NMuLi (mouse liver epithelial cells), BALB A31 3T3 HYF (mouse fibroblast cells), and MSV/MLV BALB 3T3 A31 HYF (Moloney sarcoma virus-transformed mouse fibroblast cells). The most effective quencher was the lipid-soluble N-octyl iodide, which quenched the BP emission by a factor of 6 with little change in the DE emission. At comparable molarity, methylene iodide was a relatively effective quencher for both aromatic hydrocarbons, but it was not selective. The ionic quencher KI was ineffective. The results were, in general, independent of the type of mouse cell strain. Information on the location of the hydrocarbons in the cells is given. The selectivity of n-octyl iodide may be due to the fact that collisions with BP are much more likely than collisions with the DE. Thus, the possible locations of the DE are: bound in proteins or attached near the polar head groups of lipids in membranes or attached in a nonlipid portion of the cell. The selective quenching technique should have broad application to fluorometric studies of various kinds in biological systems, including flow cytometry and cell sorting. (44 refs)

78-6330 **Health Aspects of Water Chlorination with Special Consideration of the Cocarcinogenicity of Chlorine. II. The Cocarcinogenicity of Chlorine.** (Ger) Pfeiffer, E. H. (Hygiene-Institut, Hochhaus am Augustusplatz, D-6500 Mainz, W. Germany). *Zentralbl Bakteriol [Orig B]* 166(2/3): 185-211; 1978.

The possible cocarcinogenicity of chlorine and polycyclic aromatic hydrocarbons was investigated. A 0.22% or 0.44% acetonic benzo(a)pyrene (BP) soln was applied twice weekly to the depilated skin of the backs of female NMRI mice for 10 wk to a total dose of 750 or 1,500 μg/animal. In addition, various groups were treated with a 1% NaOCl soln either before, during, or after the BP treatment. After 128 wk mor development was considerably slowed or termin prematurely in the groups given a chlorine pretreatment 750 or 1,500 μg BP and in the groups that had rece chlorine after applications of the lower BP dose. Tu growth in the remaining groups was not affected. Adm tration of chlorine before BP noticeably reduced the number of tumors considerably; only a very slight reduc was found in the remaining test groups. Chlorine treatr decreased the number of carcinomas among the tumor about 40%, regardless of the treatment method or the dosage. The mean tumor induction times were not sig cantly affected by chlorine treatment, and there were no jor differences in mortality rates among the groups. Pos mechanisms of action of chlorine are discussed. (162 r

78-6331 **Pulmonary Metabolism of Epoxides.** (Smith, B. R. (Natl. Inst. Environmental H Sciences, Research Triangle Park, NC, 27709); Maguir H.; Ball, L. M.; Bend, J. R. *Fed Proc* 37(11): 2480-2484;

Epoxide hydrase (EH) and glutathione S-transferase (G activities were measured in pulmonary tissue of guinea rabbits, and rats. On the basis of total organ activity activity per milligram of protein, pulmonary tissue had capacity to metabolize epoxides than liver tissue. Pulmo EH and GST were refractory toward inducers such as di zanthracene, pregnenolone-16α-carbonitrile, 2,3,6,7-t chlorodibenzo-p-dioxin, and phenobarbital. In the isol perfused rabbit lung, benzo(a)pyrene 4,5-oxide (BPO) metabolized by EH and GST at similar initial rates, but activity was lost after 5 min at a dose of 1 micromole (μ BPO/lung and after 15 min at 5 μmol BPO/lung. Adm tration of a second dose of BPO (2.5 μmol) 19 min after first temporarily restored the initial rate of dihydrodiol duction, indicating that the EH system itself was still f tional. EH activity is probably lost because of inadequat cal substrate levels. GST from rabbit lung cytosol separated chromatographically into six peaks contai 1-chloro-2,4-dinitrobenzene (DNCB)-conjugating acti All six peaks also displayed GST activity toward BPO two toward styrene oxide. GST isolated from rabbit supernatant fraction was also separated into six peaks, a which conjugated glutathione with DNCB and BPO, only one of which conjugated glutathione with styrene ox The liver protein and total transferase activity levels w higher than those in the lung. Each of the cell types in lungs is postulated to possess its own specific enzyme le For the detoxification defense mechanism to be effec each cell would have to be capable of metabolizing its internally generated epoxides. (25 refs)

78-6332 **Nephrogenic Hypertension and Carcinogene** (Rus) Litvitskii, P. F. (Dept. Pathologic Ph

gy, I. M. Sechenov First Moscow Medical Inst., Moscow, SR); Kogan, A. Kh. *Vopr Onkol* 24(9): 56-60; 1978.

tudy was made of the effect of nephrogenic hypertension HI), induced by left nephrectomy and stenosis of the artery he contralateral kidney, on the growth of benzo(a)pyrene P)-induced tumors and of transplanted carcinoma RS-1, coma 45, Walker's carcinosarcoma, Zajdela ascites atoma, and Walker's metastasizing carcinosarcoma in outbred male rats. BP was injected sc, the solid tumor ls were transplanted sc, and Zajdela hepatoma ascites cells re injected into the abdominal cavity. Another group of rats without NHT was treated in the same manner. NHT uced the latent period of BP-induced tumors by 21.1 days < 0.001), but it had no effect on the latent period of the nsplanted tumors. In addition, NHT increased the abso- e wt of all tumors from 33 to 41.4 g, the tumor:body wt io from 10.14 to 14.1 ($p < 0.001$), and the frequency of tastases of Zajdela ascites hepatoma and Walker's metas- izing carcinosarcoma. The findings indicate that NHT is redisposing factor for carcinogenesis, probably as a result the changes in immunological reactivity and the deficient od supply and tissue oxygenation that occur during cer- n phases of hypertension. (14 refs)

-6333 **Elevation of Hepatic Glutathione S-Transferase Activities and Protection Against Mutagenic etabolites of Benzo(a)pyrene by Dietary Antioxidants.** ng) Benson, A. M. (Dept. Pharmacology, Johns Hopkins iv. Sch. Medicine, Baltimore, MD, 21205); Batzinger, R. Ou, S. Y.; Bueding, E.; Cha, Y. N.; Talalay, P. *Cancer s* 38(12): 4486-4495; 1978.

e effects of the antioxidants 2(3)*tert*-butyl-4-hydrox- nisole (BHA) and ethoxyquin (EQ) on the mutagenic etabolites of benzo(a)pyrene (BP) were studied in female D-1 mice and male Sprague-Dawley rats injected im with 0 mg/kg BP. The mice were maintained for 12 days on ets containing 0.75% BHA or 0.5% EQ; alternatively, me mice received BHA (100 to 1,000 mg/kg/day for 4 ys) by gavage. The rats were fed a diet containing 0.75% HA for 8 days. The mutagenic activity of BP urinary etabolites for *Salmonella typhimurium* strains TA98 and A100 was markedly reduced in the presence of glutathione gether with the liver cytosols of animals fed BHA. The liver tosols of mice and rats maintained on control diets were uch less effective in this respect. Dietary BHA increased ouse and rat hepatic glutathione S-transferase (GSI) specif- activities with 1,2-dichloro -4- nitrobenzene, 1-chloro- 4-dinitrobenzene, p-nitrobenzylchloride, and δ^5-andro- ene -3,17- dione. The increases were larger (5- to -fold) in mice, and they depended on the dose and duration BHA administration. Increases in GST specific activities ere also observed in mouse hepatic cytosols after feeding of Q. Direct addition of reduced glutathione and purified ST's A and B obtained from rat liver to the mutagenicity say system mimicked the effect of the rodent cytosols. The protective effects of the two antioxidants against potent carcinogens may be due, at least in part, to their ability to elevate GTA's. These enzymes inactivate arene oxides and other hydrophobic electrophiles by catalyzing their conjugation with glutathione. (45 refs)

78-6334 **Carcinogens and Dicumarol: Opposite Effects on Rat Liver NAD(P)H Dehydrogenation.** (Eng) Schor, N. A. (Dept. Pathology, Tulane Univ. Sch. Medicine, New Orleans, LA, 70112); Boh, E.; Burke, V. T. *Enzyme* 23(4): 217-224; 1978.

The effects of four carcinogens and dicumarol (DC) on hepatic D-T-diaphorase activity were studied in several groups of Sprague-Dawley rats. Groups 1-4 received benzo(a)pyrene (BP), 7,12-dimethylbenz(a)anthracene, N-acetylaminofluorene, or DC (4.0, 3.9, 4.5, and 3.0×10^{-4} moles/kg, respectively, intragastrically) 24 hr or (DC) 24 and 48 hr before sacrifice. In Group 5, BP was administered for 6 days, DC was given on days 5 and 6, and rats were killed on day 7; in Group 6, 3-methylcholanthrene (3-MC: 7.5×10^{-5} moles/kg, ip) was given for 3 days, DC was given on day 3, and rats were killed on day 5. All carcinogens increased D-T-diaphorase activity 24 hr after administration. DC inhibited this activity, but not the aryl hydrocarbon hydroxylase activity induced by BP and 3-MC. DC potentiated the toxic effects of 3-MC and BP. None of the chemicals affected NADPH cytochrome c reductase activity. It is suggested that carcinogens stimulate two enzyme systems: the microsomal oxidases, which transform some chemicals into highly reactive and toxic compounds, and the cytosolic reductases, which may further detoxify the compounds formed in the microsomal fraction by transforming them into dihydrodiols and phenols. Apparently, there is a competition between both systems. The increase in toxicity with DC (which inhibits the cytosolic system) + BP or 3-MC is presumed due to a lack of detoxification of the two carcinogens. (19 refs)

78-6335 **Effect of Anesthetic Agent on Lung Tumor Induction in Hamsters Given Benzo(a)pyrene-Ferric Oxide.** (Eng) Henry, M. C. (Environmental Protection Res. Div., US Army Medical Bioengineering Res. and Development Lab., Ft. Detrick, MD, 21501); Port, C. D. *J Natl Cancer Inst* 61(5): 1221-1227; 1978.

Comparison was made of the effects of Brevital, ether, and methoxyflurane (MF) on lung tumor induction in noninbred Syrian golden hamsters given 10 weekly intratracheal instillations of a benzo(a)pyrene (BP)-ferric oxide mixture. Inhalation anesthesia with ether or MF was accomplished by a closed recirculatory system that allowed a short induction time and good control over the concentration of anesthetic. A third group was subjected to systemic induction with 0.4-0.8 ml of 1% Brevital soln ip. Survival rates during the 10 weekly instillations were least for the Brevital-treated

group and greatest for the MF-treated animals. Body wt gain was lower in the ether- and Brevital-treated groups than in the MF-anesthetized group. Animals anesthetized with Brevital had the shortest tumor latency, but tumor incidence was similar in this group and the group treated with ether. Exposure to MF and carcinogen produced a slow onset of deaths from tumors and a lower tumor incidence. The predominant tumor type in all segments of the respiratory tract was squamous cell carcinoma. The most common tumor sites were the trachea and bronchus. Thus, experimental conditions for the induction of lung carcinomas must be standardized if consistent and reproducible results are to be obtained. Inhalation anesthesia with ether does not appear to be the method of choice because of its irritant properties and possible effect on tumor formation. (14 refs)

78-6336 **Human Skin Aryl Hydrocarbon Hydroxylase: Induction by Coal Tar.** (Eng) Bickers, D. R. (Div. Dermatology, Case Western Reserve Univ., Sch. Medicine, Cleveland, OH, 44106); Kappas, A. *J Clin Invest* 62(5): 1061-1068; 1978.

The effect of cutaneous application of a coal tar (CT) soln (crude CT diluted to 20% with ethanol and polysorbate 80) on aryl hydrocarbon hydroxylase (AHH) activity was investigated in six patients with generalized psoriasis and three with severe atopic dermatitis. CT soln (100 μl) was applied to the skin, and the site was biopsied 24 hr later. Cutaneous AHH activity was increased two- to fivefold in treated vs untreated skin. AHH activity was also induced in human skin samples incubated with CT for 24 hr, but not to as high a level. In human skin incubated with CT in vitro, there was an initial lag phase of 8 hr followed by a 16-hr period of linearly increasing AHH activity, after which the activity diminished. Max responses both in vivo and in vitro occurred after 24 hr, and enzyme activity in vitro was time-, tissue- and substrate concentration-dependent. The application of a CT soln to neonatal rat skin resulted in a > 10-fold induction of skin AHH activity 24 hr later. Hepatic AHH activity was also markedly increased, indicating that substantial percutaneous absorption had occurred. Assay of several defined constituents of CT for AHH induction showed that benzo(a)pyrene was the most potent inducer of AHH tested followed by pyrene and anthracene. These studies indicate that topical application of CT soln in doses used to treat dermatologic disease causes induction of AHH in human skin, and they suggest that this induced enzyme activity could relate to carcinogenic responses to this agent in skin and other tissues. (44 refs)

78-6337 **The Identification of High Molecular Weight Polynuclear Aromatic Hydrocarbons in a Biologically Active Fraction of Cigarette Smoke Condensate.** (Eng) Snook, M. E. (Tobacco Lab., Agricultural Res. Service, U.S. Dept. Agriculture, P.O. Box 5677, Athens, GA, 30604); Severson, R. F.; Arrendale, R. F.; Higman, H. C.; Chort O. T. *Beitr Tabakforsch* 9(2): 79-101; 1977.

As a result of several gas chromatographic procedures, cluding gel filtration and high-pressure liquid chromatog phy, and of mass spectral, UV absorption, and chroma graphic retention data, > 200 compounds were isolated identified in the most biologically active fraction of cigare smoke condensate. Newly identified were 3,4-dimethylene rene, 3,4-trimethylenepyrene, cyclopenta(c,d)pyrene, 4,5- thylenetriphenylene, benzo(b)perylene, and several diben fluoranthenes. (21 refs)

78-6338 **Plasminogen Activator in Chick Fibroblasts: duction of Synthesis by Retinoic Acid; Syn gism with Viral Transformation and Phorbol Ester.** (E Wilson, E. L. (Dept. Clinical Science and Immunolo Medical Sch., Univ. Cape Town, Cape Town, South Afric Reich, E. *Cell* 15(2): 385-392; 1978.

The effects of vitamin A and its derivatives, the retinoids, plasminogen activator (PA) synthesis were investigated chick embryo fibroblast (CEF) cultures. Low concentrati of retinoic acid (RA: 10^{-6}-10^{-10} M) and the retinoids stimul ed PA synthesis by up to 9- or 10-fold, a level somewhat lo than that obtained with optimal concentrations of the pot tumor promoter phorbol myristate acetate (PMA). The eff of RA required protein and messenger RNA synthesis b in contrast to enzyme induction by PMA and/or sarco virus transformation, retinoid effects were not significan inhibited by elevated concentrations of cyclic AMP. The fects of RA and sarcoma virus transformation were synerg tic rather than additive in inducing and/or stimulating production. Analogous synergism was observed between and PMA, but only at suboptimal concentrations of the ter. RA had no effect on PA production in normal or tra formed cultures maximally stimulated by PMA. These fi ings may help to elucidate the role of retinoids in promoti tumor growth, tissue remodeling, and teratogenesis. (27 re

78-6339 **The Induction of Differentiation in Teratoc cinoma Stem Cells by Retinoic Acid.** (E Strickland, S. (Rockefeller Univ., New York, NY, 1002 Mahdavi, V. *Cell* 15(2): 393-403; 1978.

Plasminogen activator (PA) was used as a marker to stu the effects of a number of compounds, especially retinoi on F9 cells, a teratocarcinoma cell line that undergoes v limited differentiation under normal culture conditions. R noic acid at concentrations as low as 10^{-9} M induced multi phenotypic changes in the cultures. The molecule was creasingly effective as the concentration was raised to 10^{-6} (10^{-7} M was used in most of the experiments); above t amount, it was toxic. Retinoic acid increased PA secreti more than 10-fold in 3 days of culture. There was a concor

hange in cellular morphology, which closely resembled resumptive endoderm derived from teratocarcinoma yoid bodies. Treatment with retinoic acid alone or in ination with dibutyryl cyclic AMP (10^{-3} M) resulted in crease in intracellular PA levels that paralleled the en-d secretion of this enzyme, indicating that these com-ds do not simply increase secretion of preformed PA but e and stimulate the production of active enzyme. The ntage of colonies secreting PA was increased from < to almost 100% by retinoic acid. When cultures were d first with retinoic acid, washed well, and then treated dibutyryl cyclic AMP, the cells secreted much more PA if they were incubated with retinoic acid followed by ol medium. Retinoic acid also increased the synthesis llagenlike proteins and increased the alkaline phospha-content of the cultures by 20-fold. The nature of these ges, as well as their independence of the continued pres-of retinoic acid, are consistent with the proposition that oic acid induces differentiation of embryonal carcinoma into endoderm. (42 refs)

340 **The Effects of Organic Compounds on Mutagen- and Carcinogen-Activating Enzymes In Vi-Meeting Abstract).** (Eng) Bradshaw, J. J. (Dept. Physi- and Medical Biochemistry, Univ. Cape Town Medical Cape Town, South Africa); Ivanetich, K. M. *Mutat Res* : 154; 1978. (no refs)

341 **Fecal Hydroxysteroid Dehydrogenase Activities in Vegetarian Seventh-Day Adventist, Con-Subjects, and Bowel Cancer Patients.** (Eng) Macdonald, (Dept. Medicine, Dalhousie Univ., Halifax, Nova Sco-Canada); Webb, G. R.; Mahony, D. E. *Am J Clin* 31(10): S233-S238; 1978.

free extracts of anaerobic bacteria from the fecal prepa-ns of 14 vegetarian Seventh-Day Adventists (SDA), 8 nts with cancer of the large bowel, and 16 controls were ed for NAD and NADP-dependent 3α-, 7α-, and 12α-oxysteroid dehydrogenase (HSDA) activities using an-terone and various bile salts as substrates in eight sub-e-cofactor combinations. NADP-dependent 12α-HSDH ity was highest in the SDA, while 7α-HSDH content was icantly increased in cancer patients over controls and e so over SDA. Fecal pH values for SDA, controls, and er patients were 6.46 ± 0.58, 6.66 ± 0.62, and 7.03 ± respectively. The cancer pH was significantly higher the SDA value; and when plotted against values for 7 SDH, fecal pH segregated 7/8 cancer patients from the r groups. Parameters for NADP-dependent 3α-HSDH ities using either type substrate were correlated, and the ionship ($r = 0.72$) suggested that this enzyme can oxi-both bile salts and neutral sterols in fecal anaerobic bac-. Although 7α-HSDH is elevated in bowel cancer patients, it is presently unclear whether this enzyme is merely a marker, or plays some carcinogenic role itself. (30 refs)

78-6342 **Rat Differences in Mammary Tumor Induction with Estrogen and Neutron Radiation.** (Eng) Shellabarger, C. J. (Medical Dept., Brookhaven Natl. Lab., Upton, NY, 11973); Stone, J. P.; Holtzman, S. *J Natl Cancer Inst* 61(6): 1505-1508; 1978.

The effects of diethylstilbestrol (DES) and/or neutron radiation on mammary tumor formation were studied in female ACI and Sprague-Dawley (SD) rats. Young adult rats were given sc implants of pellets containing 5 mg DES and 15 mg cholesterol 2 days before irradiation with 0.4, 1.3, or 4.0 rads of 0.43 million electron-volt neutrons. Other rats received DES or irradiation only or no treatment; all rats were studied until death or for a max of 48 wk. DES treatment alone significantly increased the number of ACI rats (52%) with mammary adenocarcinomas (MAC) and the number of MAC/rat (2.74), but it had no effect on the SD rats. Conversely, irradiation only at 4 rads had no effect on the ACI rats, but it significantly increased the number of SD rats (32%) with mammary fibroadenomas (FAC), the number of MAF/rat, and the number of MAC/rat. Combining DES and irradiation 4 rads increased MAC incidence in ACI rats (91%), the incidence of multiple MAC (≥ 16 tumors) (65%), and the number of MAC/rat (15.10) to a total larger than the sum of the effects of the individual agents. Combined treatment in SD rats decreased MFA incidence (3%) and the number of MFA/rat (0.03) to values lower than irradiation alone. Additionally, DES treatment produced large pituitary tumors in 78%-100% of ACI rats and pyometritis in 53% of SD rats. Thus, DES and neutron irradiation acted synergistically on MAC formation in ACI rats but not in SD rats. (15 refs)

78-6343 **Perphenazine and Testosterone Metabolism by Mammary Tumours in Oophorectomized Rats.** (Eng) Buchan, P. (Dept. Clinical Surgery, Medical Sch., Univ. Edinburgh, Edinburgh EH8 9AG, Scotland); Miller, W. R. *Biochem Soc Trans* 6(1): 135-136; 1978.

The effects of prolactin and ovarian hormones on tumor growth and steroid metabolism were studied in female Sprague-Dawley rats with 7,12-dimethylbenzanthracene-induced (30 mg intragastrically) mammary tumors. When the tumors reached a size of > 2 cm x 2 cm, the animals were oophorectomized and placed in one of two groups. The treatment group received daily sc injections of 5 mg/kg perphenazine, and the control group received the vehicle only; all animals were killed 14 days later. Oophorectomy alone produced an immediate regression of all tumors, but the combined treatment resulted in a variable response: certain tumors increased in size while others regressed, usually after a short period of growth. Animals from the treatment group showed a signifi-

cantly higher metabolism of testosterone than controls. However, the major metabolites of testosterone in groups were 5α-dihydrotestosterone and 5α-androstanediol. Thus, in oophorectomized animals, perphenazine does not produce the stimulatory effects on mammary tumor growth and steroid metabolism that it has been shown to do in endocrine-intact animals. (3 refs)

78-6344 **Attempted Induction of Granulosa Cell Tumor in Balb-C Mice by Gonadotropin Administration.** (Eng) Menczer, J. (Dept. Obstetrics and Gynecology, Sheba Medical Center, Tel-Hashomer, Israel); Komarov, H.; Shenboum, M.; Insler, V.; Czernobilsky, B. *Gynecol Invest* 8(5/6): 314-322; 1977.

An attempt of granulosa cell tumor (GCT) induction by prolonged administration of exogenous pregnant mare's serum gonadotropin (PMSG) to young (21-day-old), mature (6-mo-old), and middle-aged (10-mo-old) BALB/c mice resulted mainly in stromal luteal cell proliferation. This proliferation occurred in 48.9% of young mice, 64.5% of mature mice, and 65% of middle-aged mice. The effect seemed to depend on duration of treatment in young mice. Young mice inoculated for <6 mo developed significantly less luteal cell proliferation than those inoculated for >6 mo. Only one GCT was found. This study supports the contention that besides gonadotropin stimulation, other factors may be involved in GCT development. A large number of PMSG-inoculated mice developed generalized lymphosarcoma, the mechanism of which remains unknown. (15 refs)

78-6345 **Covalent Binding of Ethinylestradiol and Estrone to Rat Liver DNA In Vivo.** (Eng) Jaggi, W. (Inst. Toxicology, Federal Inst. Technology and Univ. Zurich, CH-8603 Schwerzenbach, Switzerland); Lutz, W. K.; Schlatter, C. *Chem Biol Interact* 23(1): 13-18; 1978.

The covalent binding of 6,7-^{3}H-ethinylestradiol (EE) and 6,7,-^{3}H-estrone (E) to the liver DNA of fasted female Sprague-Dawley rats (190 to 240 g) was measured 8 hr after the administration of 80 μg (9.2 mCi) of the estrogens by gavage. Only 1% of the total radioactivity from EE was excreted in the urine within 8 hr; 4% of the radioactivity lyophilized as tritiated water. Three percent of the radioactivity from E was excreted in the urine within 8 hr, 3% of it as tritiated water. The binding of EE and E to the liver DNA was 1.5 and 1.1, respectively, expressed as binding to DNA/dose, in units of μmoles hormone/mol DNA phosphate/millimoles hormone/kg. It was on the same order of magnitude as that for benzene and about 10,000-fold lower than that for typical liver carcinogens such as aflatoxin B_1 and N,N-dimethylnitrosamine. E and its ethinyl derivative should not differ with regard to their suspected carcinogenicity. (20 refs)

78-6346 **Histometric Study of the Pituitary in … Treated Neonatally with Steroids and the … tionship Between Prolactin Cells and Mammary Tu… genesis.** (Eng) Kawashima, S. (Zoological Inst., Fa… Science, Univ. Tokyo, Tokyo 113, Japan); Bern, H. A.; J… L. A.; Mills, K. T. *Endocrinol Jpn* 25(4): 341-348; 197…

In female BALB/cfC3H/Crgl mice, neonatal hormone t… ments had a significant effect on pituitary histology … mammary tumorigenesis. Within 36 hr after birth, mice … given five daily sc doses of 5 or 20 μg 17β-estradiol (E… 100 μg progesterone (PRG), or 5 or 20 μg ovine prol… (PRL), singly or in various combinations. Pituitary gl… were studied at autopsy upon tumor development or a… 1 yr. Treatment with ESD (with or without PRL), PRG … ESD + PRG resulted in significantly greater overall n… mary tumor incidence, at a significantly earlier age, th… untreated controls. Pituitary PRL cells were more num… in tumor-bearing mice vs non-tumor-bearing mice. Ova… tomy at day 40 markedly decreased the PRL cell count … abolished the effects of neonatal steroid treatment. Neo… ESD (with or without PRL) and PRG treatment also res… in significant decreases in gonadotropes. PRL alone ha… such effect. There was correlation between gonadotrop… thyrotrope levels and mammary tumor incidence. Thes… sults suggest that neonatal steroid treatment stimulates n… mary tumorigenesis through increased prolactin secre… (34 refs)

78-6347 **Induction of Ovalbumin Synthesis in Imm… Chicks by Actinomycin D and Thioacetar…** (Eng) Sharma, O. K. (Dept. Microbiology, Univ. Colo… Medical Center, Denver, CO, 80262). *Science* 202(4… 68-69; 1978.

The induction of ovalbumin synthesis and of an increa… serum progesterone (PG) levels in estrogen-treated imm… chicks by thioacetamide (TAM) and actinomycin D (A… is reported. Four-day-old Calhorn chicks were inoculate… with 1 mg estradiol benzoate in sesame oil for 10 days … mary estrogen stimulation). After 3-4 wk of estrogen … drawal, with no ovalbumin synthesis being detectable, c… were inoculated ip with TAM (0.25 mg/g/day x 3) or … AMD (0.4 μg/g/day x 1). TAM-treated chicks were s… iced after 3 days, AMD-treated chicks after 24 hr. Ovi… were removed, and ovalbumin synthesis in the oviduct … num was determined. Labeled ovalbumin was measure… specific immunoprecipitation with monospecific antis… against purified ovalbumin and confirmed by gel ele… phoresis. Pooled serum was analyzed for PG by radi… munoassay. TAM and AMD induced ovalbumin synt… from undetectable percentages of total protein synthes… 9.1% and 8.7%, respectively. Likewise, serum PG l… (nanograms/100 mg) were increased from 89 to 296 and … 40 to 317 in two TAM treatment trials and from 100 to … and from 81 to 496 in two AMD trials. PG induced by T… and AMD may account for the induction of ovalbumin …

s. How carcinogens of different structures such as TAM AMD increase serum PG remains to be elucidated. The one imbalance may have implications in the mechns of carcinogenesis. (27 refs)

348 **Metabolism of Androgens and Estrogens by Human Fecal Microorganisms.** (Eng) Lombardi, P. ctious Disease Service, Dept. Medicine, Tufts-New Eng- Medical Center, Boston, MA, 02111); Goldin, B.; Bou- E.; Gorbach, S. L. *J Steroid Biochem* 9(8): 795-801; 1978.

metabolism of androgens and estrogens by human fecal oorganisms was studied in vitro at high and low fecal act concentrations and under aerobic and anaerobic conns. The reactions were run for 0-7 days at a fecal extract entration of 50-60 or 6-10 mg/ml; the metabolites were acted and purified, and steroids were identified by gas-liqchromatography. In reactions at the high fecal concentra- 5β-3-ketosteroids were reduced to 5β-3-hydroxyds and 17-ketoandrogens and estrogens were reduced to hydroxy products. A low fecal concentration resulted in ucts formed by oxidation and by cleavage of conjugated ids: 5β-androstane-3,17-dione was converted to 4-antene-3,17-dione, and 17β-hydroxysteroids were convert- 17-oxosteroids. Estrogen-3-sulfate and estradiol-3-glunide were hydrolyzed to form estrone and estradiol, ectively. These results indicate that fecal concentration rmines the types of metabolites formed. The reactions rred under aerobic and anaerobic conditions. Their ocence under aerobic conditions may reflect the ability of fecal extract to lower the oxidation-reduction potential e reaction mixture. This study demonstrates that human tinal flora can carry out a variety of reductive, oxidative, hydrolytic reactions on androgens and estrogens. (21

349 **Plasma Hormone Profiles of Young Women at Risk for Familial Breast Cancer.** (Eng) Fish- J. (Inst. Steroid Res., Montefiore Hosp. and Medical ter, Bronx, NY, 10467); Fukushima, D.; O'Connor, J.; enfeld, R. S.; Lynch, H. T.; Lynch, J. F.; Guirgis, H.; oney, K. *Cancer Res* 38(11, part 2): 4006-4011; 1978.

ma hormone profiles from 30 women at high risk for lial breast cancer and from their matched low-risk con- were analyzed. The case subjects were premenopausal, pubertal women without evidence of neoplastic disease with many close relatives with breast cancer or tumors ciated with breast cancer and who, by genetic analysis, e at a clearly defined high risk for the disease. The con- were matched closely for height, wt, age, and reproduchistory. Plasma hormone levels were measured every secday throughout the menstrual cycle, and the results were yzed in terms of follicular, luteal, and full-cycle mean entrations. There were no statistically significant differences in prolactin, follicle-stimulating hormone, luteinizing hormone, estrone, estradiol, or estriol levels between the two groups, although the high-risk group had consistently lower values of all these hormones except estriol. The mean plasma estriol levels in the follicular and luteal stages were 19.7 and 24.8 picograms/ml in the high-risk women and 23.5 and 23.1 picograms/ml in the controls. The results suggest that the etiology of female and male familial breast cancer is fundamentally different, since male relatives of male breast cancer patients had substantially elevated plasma estrogen levels. (26 refs)

78-6350 **Phytoestrogen Interaction with Estrogen Receptors in Human Breast Cancer Cells.** (Eng) Martin, P. M. (Institut J Paoli-I. Calmettes, 13273 Marseille, France); Horwitz, K. B.; Ryan, D. S.; McGuire, W. L. *Endocrinology* 103(5): 1860-1867; 1978.

The interactions of phytoestrogens with estrogen receptors (ER) were studied in the human breast cancer cell line MCF-7. When cytosol from MCF-7 cells was incubated with 4 nanomoles (nmol) ^{3}H-estradiol and 400 nmol unlabeled phytoestrogens, all but one compound competed with estradiol for binding to nuclear and cytoplasmic ER. The relative binding affinities (followed by approx dissociation constants) were zearalenol high-melting point isomer (HP) (1 nmol) > zearalenol low-LMP (15 nmol) > zearalenone (6 nmol) = coumestrol (2 nmol) > genistein (10 nmol) > formononetin (2 μM), which had little effect. The phytoestrogens bound only weakly to sex steroid-binding globulin and none bound to corticosteroid-binding globulin. When whole MCF-7 cells were incubated with 1 μM genistein, coumestrol, and zearalenol HMP for 5 min to 15 hr, the cytoplasmic ER was depleted within 5 min, and the hormone-receptor complex was translocated to the nucleus. Zearalenol was as effective as estradiol in the ER translocation. The phytoestrogen-bound receptors were processed in the nucleus at about the same rate as estradiol-bound receptor. The plant estrogens, particularly coumestrol, were markedly enhanced during the log-phase growth of MCF-7 cells. These nonsteroidal compounds apparently function in the same manner as estrogen, and they may have profound effects on estrogen target cells. (41 refs)

78-6351 **Impeding Estrogens and the Etiology of Breast Cancer.** (Eng) Wotiz, H. H. (Dept. Biochemistry, Boston Univ. Sch. Medicine, Boston, MA, 02118); Chattoraj, S. C.; Kudisch, M.; Muller, R. E. *Cancer Res* 38(11, part 2): 4012-4020; 1978.

New data relevant to the action of estriol (E) and related impeding estrogens, obtained from several experiments, are presented. Synthesis of progesterone receptor, induced by 2-day treatment of Sprague-Dawley rats with estradiol (ED: 0.1 μg/day/sc), was inhibited by simultaneous injection of 10 μg/day E or 16-epiestriol. Silastic tubing implants con-

taining E (1 mg) markedly reduced breast tumor takes and delayed the onset of first tumors in rats treated 4 days later with 7,12-dimethylbenz(a)anthracene (3 mg every other day x 3, iv). In contrast, implants containing 1 mg ED appeared to increase the number of tumor-bearers and to accelerate the onset of first tumors. Administration to pregnant rats of antibody specific to ED or E during gestation days 11-14 resulted in a slight reduction in the number of offspring for anti-ED antibody but a nearly total loss of fetuses with anti-E antibody. The contraceptive function of E cyclopentyl ether (500 μg/kg po, gestation day 1) was reversible when 1.2 μg/kg ED, was injected sc on gestation day 4. Injection of freshly mated rats with up to 500 μg/kg 2-hydroxyestrone sc did not result in any antiimplantational or estrogenic activity. However, topical insertion of Silastic tubing implants containing this steroid into rabbit uteri produced complete contraceptive effects. Multiple injections of 50 μg 2-hydroxyestrone produced max uterine growth in immature and adult ovariectomized rats. The data suggest that E, although containing some estrogenic properties, must have a significantly different physiological role in cancer development and reproduction when present in appropriate admixture with ED. (43 refs)

78-6352 **Benign Liver Tumors and Oral Contraceptives.** (Eng) Aungst, C. W. (Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263). *NY State J Med* 78(12): 1933-1934; 1978.

A hepatic adenoma developed in two women (both aged 24) who had been taking oral contraceptives for up to 4 yr and in one woman (aged 52) who had been taking conjugated estrogens for menopausal symptoms for 3 yr. One of the young women had symptoms suggesting an amebic abscess. She also had a carcinoembryonic antigen level of 18.7 nanograms/ml, a finding that may have been fortuitous. (7 refs)

78-6353 **Hepatocellular Carcinoma Associated with Oral Contraceptives.** (Eng) Menzies-Gow, N. (Central Middlesex Hosp., Acton Lane, London, England). *Br J Surg* 65(5): 316-317; 1978.

A primary hepatic tumor occurred in a 36-yr-old woman who had been taking oral contraceptives (norethisterone acetate 3 mg, ethinylestradiol 50 μg) for 6 yr. The patient suffered also from anemia and lactic acidosis. A partial hepatectomy was performed, and a secondary mass of tumor-containing lymphatic tissue in the region of the celiac axis was also excised. The tumor was a well-differentiated hepatocellular carcinoma with highly vascular areas and evidence of vascular invasion. The secondary tumor was histologically similar to the hepatocellular carcinoma. This case is the first with histological evidence of secondary spread of a malignant tumor associated with oral contraceptives. (13 refs)

78-6354 **Liver Adenoma Associated with Oral C traceptive Pill Administration.** (Eng) Baker L. (Univ. Chicago, Box 400, 950 E. 59th St., Chicago, 60637); Paloyan, D.; Simonowitz, D.; Lipson, R. M. *A Dig Dis* 23(5, Suppl): 53s-58s; 1978.

The case of a 33-yr-old woman with liver adenoma in wl an elevated serum alkaline phosphatase level led to the d nosis is reported. The patient had been taking an oral c traceptive, Ovulen 21 (0.1 mg mestranol and 1.0 ethynodiol diacetate) continuously for 11 yr. (43 refs)

78-6355 **Hepatic Estrogen and Progesterone Recep in an Estrogen-associated Hepatic Neopls** (Eng) Macdonald, J. S. (Div. Medical Oncology, Vincen Lombardi Cancer Res. Center, Washington, DC, 200 Lippman, M. E.; Woolley, P. V.; Petrucci, P. P.; Schein S. *Cancer Chemother Pharmacol* 1(3): 135-138; 1978.

The presence of cytosol estrogen and progesterone binc proteins in an estrogen-associated hepatic neoplasm was termined. The patient was a 53-yr-old premenopausal Ca sian woman who had received weekly im injections of diet stilbestrol for 1 yr to control menstrual irregularity, 2 before diagnosis of a polyploid vascular hepatic tumor 8 cm), and daily doses of an oral contraceptive contai norethynodrel + mestranol for 3 mo, 5 yr before diagn Histologically, the tumor was classified as a focal nod hyperplasia of the liver. It was found to contain high-affi receptors for estradiol (binding capacity, 47.9 f tomoles/mg protein) and progesterone (binding capacity, femtomoles/mg protein), with the binding capacity of former being three times greater than that of normal li These results are consistent with the hypothesis that a sr portion of normal hepatic cells have relatively high conc trations of cytosol estrogen receptors; these receptors ren the cells particularly susceptible to stimulation to a neopla state by estrogen. (16 refs)

See also:

*(Rev.): 78-6001, 78-6002, 78-6003, 78-6004, 78-6
78-6606, 78-6007, 78-6008, 78-6009, 78-6
78-6011, 78-6012, 78-6013, 78-6014, 78-6
78-6016, 78-6017, 78-6018, 78-6019, 78-6
78-6021, 78-6022, 78-6023, 78-6024, 78-6
78-6027, 78-6028, 78-6031, 78-6034, 78-6
78-6038, 78-6048, 78-6051, 78-6053, 78-6
78-6055, 78-6066, 78-6096.

*(Phys.): 78-6356, 78-6358, 78-6359, 78-63
78-6362, 78-6368, 78-6375, 78-63

*(Viral): 78-6395, 78-6411, 78-6426, 78-6440, 78-64

*(Immun.): 78-6490.

*(Path.): 78-6509, 78-6529.

*(Epid.-Biom.): 78-6549, 78-6550, 78-6552, 78-65
78-6556, 78-6557, 78-6561, 78-65
78-6566, 78-6567, 78-6574.

56 **Greater Promotion in Sister Chromatid Exchanges by Trimethylpsoralen than by 8-Methoxypsoralen in the Presence of UV-Light.** (Eng) Gaynor, (Dept. Dermatology, Yale Univ. Sch. Medicine, 333 St., New Haven, CT, 06510); Carter, D. M. *J Invest atol* 71(4): 257-259; 1978.

thoxypsoralen (8-MOP) and 4,5′,8-trimethylpsoralen P) were compared with respect to their ability to pro- sister chromatid exchanges (SCEs) in normal human cytes exposed to UV light (365 nanomoles). With either ical treatment, leukocytes had more SCEs than untreat- ntrols. TMP consistently induced more SCEs per cell did equal concentrations of 8-MOP. The increase in was proportional to drug concentration (3.23×10^{-7} or 10^{-8} M) and dose of UV light (0.3, 0.6, or 0.9 joule/cm^2). ment with khellin plus UV light also caused a dependent increase in the number of SCEs per cell; how- the number of SCEs was not increased at the higher ntration of this drug. No chromosomal aberrations observed with any of the treatments, but there were mitoses in cells receiving higher doses of drug and long- osures to UV light than in controls. The differences in fects of 8-MOP and TMP on various cell functions may lated to qualitative and quantitative differences in the products they form. (22 refs)

357 **Nucleosome Rearrangement in Human Chromatin During UV-induced DNA Repair Synthesis.** Smerdon, M. J. (Dept. Pathology, Washington Univ. Medicine, St. Louis, MO, 63110); Lieberman, M. W. *Natl Acad Sci USA* 75(9): 4238-4241; 1978.

osome rearrangement was investigated in human di- fibroblasts (IMR-90 cells) prelabeled with ^{14}C-thymi- during the logarithmic phase, grown to confluence, d with hydroxyurea, and irradiated with a UV dose of les/m^2. Immediately after irradiation, the cells were -labeled with ^{3}H-thymidine (10 or 90 min) and chased nradioactive medium for different times, and the distri- n of UV-induced DNA repair synthesis in chromatin neasured. Immediately after irradiation, repair synthesis rred primarily in staphylococcal nuclease-sensitive re- of chromatin. Subsequent incubation of cells in unla- medium resulted in the conversion of many of these r sites to nuclease-resistant regions. Agarose gel data ated that repair sites acquired nuclease resistance with appearance in core DNA. Rearrangement also resulted more uniform distribution of repair sites in linker and regions and not in an overrepresentation of repair syn- s in the latter. Rearrangement was both rapid and extensive: at least 85% of the repair sites underwent rearrangement during the first few hours; the rest of the repair sites underwent rearrangement at a much slower rate. There was a striking correlation between the time course of rearrangement and repair synthesis, suggesting that nucleosome rearrangement may be induced by the repair process or that the rate of repair synthesis may be regulated by nucleosome rearrangement. (14 refs)

78-6358 **Molecular Mechanisms Involved in the Production of Chromosomal Aberrations. I. Utilization of Neurospora Endonuclease for the Study of Aberration Production in G2 Stage of the Cell Cycle.** (Eng) Natarajan, A. T. (Dept. Radiation Genetics and Chemical Mutagenesis, State Univ. Leiden, Wassenaarseweg 72, Leiden, Netherlands); Obe, G. *Mutat Res* 52(1): 137-149; 1978.

A study was made of the effect of Neurospora endonuclease (NE) on the induction of single-strand (ss) breaks in the G2 stage of the cycle of Chinese hamster ovary cells by x-rays, UV light, or chromosome-breaking chemicals. The enzyme was added in the presence of inactivated Sendai virus, which mediated the introduction of NE into living cells. NE is ss-specific and thus is expected to induce double-strand (ds) breaks in the ss regions of DNA. Addition of NE + virus immediately after treatment of the cells with 50-200 R x-rays more than doubled the frequencies of breaks and exchanges compared with x-irradiated controls. The effect was dose-dependent. This increase was due to the conversion of some of the x-ray-induced ss breaks into ds breaks by NE. NE + virus increased the number of aberrations produced by methyl methanesulfonate (0.01%) and bleomycin (10 μg/ml), but not those produced by UV light (10-50 ergs/mm^2) or mitomycin C (mmc: 2 μg/ml). Addition of Micrococcus endonuclease and NE to the cells also did not alter the frequencies of UV-induced aberrations. The failure to convert UV- and MMC-induced lesions into aberrations in G2 indicated that these agents need an S-phase-dependent misreplication for aberration development. The study shows that the basic structure involved in chromosome aberrations is DNA, ds breaks lead to chromosome aberrations, and that the introduction of repair enzymes into living cells offers a way to probe into the molecular events of chromosome aberration formation. (16 refs)

78-6359 **Effects of Chemical and Physical Mutagens on the Frequency of a Large Genetic Duplication in *Salmonella typhimurium*. I. Induction of Duplications.** (Eng) Hoffmann, G. R. (Natl. Inst. Environmental Health

Sciences, Research Triangle Park, NC, 27709); Morgan, R. W.; Harvey, R. C. *Mutat Res* 52(1): 73-80; 1978.

A simple selection procedure for detecting *Salmonella typhimurium* strains that are merodiploid (MD) for almost one-third of the chromosome is based on improved utilization of L-malate as the sole carbon source in MD strains. The spontaneous frequency of the duplication in haploid strains is approx 10^{-4} per cell plated. Following the exposure of a haploid strain to mutagenic agents, there is a dose-dependent increase in the duplication frequency above the spontaneous level. X-rays, UV light, ethyl methanesulfonate, nitrous acid, and the azaacridine half-mustard ICR-372, a group of mutagens that have a variety of different molecular mechanisms of action, induced genetic duplications. It is concluded that this effect in bacteria may be a consequence of the recombinogenicity of mutagenic agents analogous to that previously noted in yeasts. (32 refs)

78-6360 **Effects of Chemical and Physical Mutagens on the Frequency of a Large Genetic Duplication in *Salmonella typhimurium*. II. Stimulation of Duplication-Loss from Merodiploids.** (Eng) Hoffmann, G. R. (Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC, 27709); Morgan, R. W.; Kirven, R. *Mutat Res* 52(1): 81-86; 1978.

Strains of *Salmonella typhimurium* (ST) that contain a duplication of approx 30% of the genome may be obtained by a simple selective procedure. These strains are very unstable, losing the duplication when grown on nonselective medium. The system used to detect duplication formation and loss is based upon clone morphology and rates of growth on L-malate. Most Salmonella derived from wild-type strain LT2 grow very poorly on medium in which L-malate is the sole carbon source, but merodiploid (MD) derivatives of these bacteria exhibit improved growth on minimal malate medium. MD's are also distinguishable from haploids by of their characteristic rough colony morphology on minimal malate or minimal glucose medium. Treatment of MD bacteria with mutagenic agents stimulated the rate at which haploid segregants were obtained from MD strains. The mutagens tested for this effect were x-rays, UV light, ethyl methanesulfonate, and the azaacridine half-mustard ICR-372. Although other models for the induction of duplication loss in MD Salmonella strains cannot be ruled out, the variety of molecular mechanisms of genetic activity exhibited by these mutagens point to a recombinational effect analogous to induced mitotic recombination in yeasts. (21 refs)

78-6361 **Does Ultraviolet Light Enhance Postreplication Repair in Mammalian Cells?** (Eng) Painter, R. B. (Lab. Radiobiology, Univ. California, San Francisco, CA, 94143). *Nature* 275(5677): 243-245; 1978.

The results of a previous study in which Chinese hamster cells were exposed twice to UV and their DNA was anal by alkaline sucrose gradient velocity sedimentation were firmed, but an alternative interpretation of the data is sented. The previous work postulated the existence of a hanced postreplication repair system to explain the alt pulse-chase profiles observed for the DNA of mamm cells irradiated with 2.5 joules (J)/m² of UV light 2 hr b a second exposure to 5.0 J/m². If the profiles are plotte total radioactivity per fixed number of cells, the inhib of DNA synthesis caused by each treatment is demonstr Analysis of profiles of both pulse-labeled and pulse-ch DNA indicated that cells exposed to 2.5 J/m² had not re ered from the damage in their DNA by 2.5 hr after irr tion. The status of nascent DNA molecules in these ce not the same as in controls; although the mol wt of nascent DNA molecules was lower in treated cells tha control cells, a significant number of these molecules h higher mol wt. Thus, the effects of 5.0 J/m² of UV ligh DNA synthesis and of maturation of nascent Chinese h ster V79 DNA are different in cells that were irradiated earlier with 2.5 J/m² than in previously unirradiated c These differences can be explained entirely by the dama effects of the first exposure, which cause an abnormal d bution of sizes of nascent DNA molecules at the tim irradiation with 5.0 J/m². (4 refs)

78-6362 **Chromosome Damage and DNA Repair Ind in Human Fibroblasts by UV and Choles Oxide.** (Eng) Parsons, P. G. (Queensland Inst. Medical Herston, Queensland, Australia); Goss, P. *Aust J Exp Med Sci* 56(part 3): 287-296; 1978.

Attempts were made to transform normal melanoma-derived human fibroblasts using UV light, ch terol oxide (ChO), and hyperthermia (40 C), singly or in c bination. Chromosome and DNA damage was monit along with transformed foci. No evidence of transforma was obtained after any of the treatments. Chromosome a rations were induced by UV light (9.8%) and ChO (8. alone, and the number of aberrations was increase 13%-20% when hyperthermia was combined with and/or UV light and to 15% when ChO and UV light combined. All the induced aberrations were still present 8 wk. Aberration frequencies were not significantly incre by multiple as opposed to single UV light treatment. UV and ChO also induced DNA repair synthesis, and the for but not the latter, induced single-strand breaks and inhib thymidine incorporation. The data suggest that factors nergistic to the later stages of carcinogenesis might be e tive long after UV exposure. (22 refs)

78-6363 **Anaplastic Thyroid Carcinoma Follow Low-Dose Irradiation.** (Eng) Komorowski, A. (Dept. Pathology, Medical Coll. Wisconsin, 8700 W. consin Ave., Milwaukee, WI, 53226); Hanson, G. A.; Ga cis, J. C. *Am J Clin Pathol* 70(2): 303-307; 1978.

2-yr-old man underwent surgical removal of a metastatic, -differentiated papillary adenocarcinoma of the thyroid r after treatment with low-dose irradiation for adenoid blems. Fifteen months later, an enlarged cervical node npted a second surgical exploration and a modified, neck dissection was performed. Histologic examination aled that a portion of the lesion was identical to the origi- tumor but that the majority of the lesion was an anaplastic dle cell tumor. Five of the 60 lymph nodes in the dissec- contained well-differentiated papillary carcinoma. Three ths postoperatively, 0.5 cm nodules were again palpated he left neck. It appears that radiation-induced thyroid inomas, in at least a very small number of people, may ssociated with aggressive carcinoma. (14 refs.)

6364 **Apurinic and/or Apyrimidinic Endonuclease Activity in Ataxia Telangiectasia Cell Extracts.** g) Sheridan, R. B. (Dept. Biochemistry, Johns Hopkins v., Sch. Hygiene and Public Health, 615 N. Wolfe St., timore, MD, 21205); Huang, P. C. *Mutat Res* 52(1): -136; 1978.

hypothesis that a defective repair mechanism for ionizing iation-induced DNA damage is associated with ataxia ngiectasia (AT) was investigated with the use of six AF three control lines. The base excision repair mechanism the apurinic and/or apyrimidinic endonuclease pu/Apy EN) responsible for incision at the site of base noval were examined in a nicking assay for Apu/Apy activity using double-stranded, covalently closed, ertwisted Φ X174 RFI DNA modified to produce an of one Apu site/molecule. There was no statistical ference in acid phosphatase levels (chosen as an ernal control) between the AT and control lines, but u/Apy EN activity was slightly reduced in the former 5 units, vs 214 units in control lines). However, even lowest level of activity seen was far in excess of that ded by a growing cell. Next, the extent of incision the Apu/Apy EN of each of the cell lines was measured a function of increasing amounts of damage in the sub- te. As the number of Apu sites increased, both control AT lines appeared capable of incising all those present. us, AT cells complete the incision step to the same extent controls, even with 22% less enzyme activity. It is conclud- that a deficiency in base excision repair at the level of the specific for the site of base loss is probably not an explana- n for AT. (24 refs)

6365 **Fatal Long-Term Sequela Following Radiation "Cure" for Ependymoma.** (Eng) Bachman, D. Johns Hopkins Hosp., Baltimore, MD); Ostrow, P. T. *Ann urol* 4(4): 319-321; 1978.

case of glioblastoma or severe radiation-induced enceph- pathy occurred at the site of an ependymoma that had n treated by radiotherapy 5 yr previously. The patient, a l, had been treated at age 13 mo with 3,960 rads to the ole brain over 6 wk followed by 2,300 rads to the spinal cord over 6 wk. It seems likely that the changes were radiation-induced. (11 refs)

78-6366 **Non-enzymatic DNA Strand Breaks Induced in Mammalian Cells by Fluorescent Light.** (Eng) Bradley, M. O. (Lab. Molecular Pharmacology, Developmental Therapeutics Program, Div. Cancer Treatment, NCI, NIH, Bethesda, MD, 20014); Erickson, L. C.; Kohn, K. W. *Biochim Biophys Acta* 520(1): 11-20; 1978.

The relationship between the mutagenicity and toxicity of fluorescent light and the production of DNA damage was examined in male Chinese hamster lung (V-79-4) cells. The cells were irradiated with 5.4 joules/m^2/sec of fluorescent light in complete medium at 1 C for 1, 2, or 3 hr. The light induced 0.041 single-strand break/10^8 daltons/hr in the DNA of the cells (4.8×10^{-6} break/10^8 daltons/joule^{-1}m^2). The breaks were unrelated to pyrimidine dimers and were also apparently distinct from previously described chemically induced alkaline-sensitive lesions. They were presumably generated by nonenzymatic mechanisms, as shown by the facts that (1) the breaks were produced at 1 C, a temperature at which most enzymatic reactions are slow; (2) the number of breaks remained constant at 1 C for 2 hr after illumination, showing no delay between illumination and break production; and (3) the breaks were produced by fluorescent light in DNA isolated from cells that were lysed and deproteinized under conditions in which no enzymes should survive. The light probably produced the breaks by a nonenzymatic mechanism either directly in the DNA itself or by the action of some unknown sensitizer. When the cells were incubated at 37 C, the breaks rejoined within 2 hr. At least two lesions were responsible for the observed effects. One had the ability to break DNA subsequently treated with alkali but was neither toxic nor mutagenic. This lesion was due to > 350-nanometer (nm) light. The other lesion(s) produced mutagenicity and/or toxicity but did not necessarily produce strand breaks. This lesion(s) was due to < 350-nm light. (21 refs)

78-6367 **The Determination of Plutonium in Tissue by Aliquat-336 Extractions.** (Eng) Fisenne, I. M. (Environmental Measurements Lab., U.S. Dept. Energy, New York, NY, 10014); Perry, P. M. *Radiochem Radioanal Lett* 33(4): 259-264; 1978.

A rapid, reproducible method based on solvent extraction was developed to separate plutonium from environmentally exposed human tissue. Tetravalent Pu was extracted from 8.5 N HNO_3 into a 30% Aliquat-336 (methyl tricaprylyl ammonium chloride)/toluene mixture. Uranium and thorium were removed by nitric and hydrochloric acid washes, and the Pu was back-extracted with an HCl-HF soln. Electrodeposition of Pu from an acidic ammonium sulfate soln produced a plate suitable for alpha spectrometry. The amount of Pu recovered from samples of human lung, bronchial tree, and bone was 70%-80%, indicating that the

chemical yield was consistent regardless of tissue type or wt of tissue analyzed. (6 refs)

78-6368 **The Use of Transposable Genetic Elements in *Drosophila melanogaster* as a Fast and Sensitive System for Mutagenicity Testing (Meeting Abstract).** (Eng) Rasmuson, B. (Dept. Genetics, Univ. Umea, S-901 87 Umea, Sweden); Svahlin, H.; Rasmuson, A.; Montell, I.; Olofsson, H. *Mutat Res* 53(2): 252; 1978. (no refs)

78-6369 **$^{239}PuO_2$ Aerosol Inhalation Exposure of Miniature Swine.** (Eng) Karagianes, M. T. (Biology Dept., Battelle, Pacific Northwest Labs., Richland, WA, 99352); Beamer, J. L.; Clary, A. J.; Craig, D. K.; Decker, J. R.; Cannon, W. C. *Radiat Res* 74(1): 79-87; 1978.

Because of the anatomic and physiological similarities between swine and humans, techniques were developed for the inhalation exposure of miniature swine to radioactive aerosols to determine the biological effects of $^{239}PuO_2$. Anesthetized animals were exposed to $^{239}PuO_2$ aerosols in dog inhalation chambers that had been modified to accommodate the swine. A sling cart for transporting and restraining the pigs and special face masks to allow intranasal exposure only were designed and fabricated. Four swine were exposed to aerosols consisting of 20 mg ^{239}Pu/ml water and an air mixture of 5:1. Two swine were exposed to aerosols having an activity median aerodynamic diameter (AMAD) of 3.0 μm and a geometric standard deviation (GSD) of 2.1, and two were exposed to aerosols with an AMAD of 2.0 μm and a GSD of 1.8. The pigs were killed at 10, 13, 30, and 90 days postexposure. Pu was cleared from the body in a biphasic pattern, with a biological retention half-time of a few days for 90% of the initial alveolar burden and $\geq$50 days for the remainder. There was very little transfer of Pu to the systemic organs: 83%-96% of the Pu retained in the body at necropsy was in the lung and pulmonary lymph nodes. (20 refs)

78-6370 **Frequency of α-Particles from $^{239}PuO_2$ in Lung Cells.** (Eng) Kellerer, A. M. (Institut fur Medizinische Strahlenkunde der Universitat Wurzburg, Versbacher Landstrasse 5, D-8700 Wurzburg, W. Germany). *Radiat Environ Biophys* 15(11): 13-19; 1978.

Mathematical considerations of the effect of $^{239}PuO_2$ particles in the lung are presented. If a given activity is uniformly dispersed, a max number of cells will be traversed by α-particles and the probability of multiple traversals of one cell will be small. However, if the activity occurs in $^{239}PuO_2$ particles, the cells close to these particles will be subject to multiple traversals and the number of cells at risk will be reduced. Furthermore, malignant transformations produced by the α-particles are less likely to be expressed because it is unlikely that multiply traversed cells will retain their proliferative capacity. It is thus concluded that a given activity will be less effective when it occurs in $^{239}PuO_2$ particles. (4 refs)

78-6371 **Endonuclease Activities from a Permane Established Mouse Cell Line that Act U DNA Damaged by Ultraviolet Light, Acid and Osmium roxide.** (Eng) Nes, I. F. (Dept. Biochemistry, Univ. Ber Arstadveien 19, 5000 Bergen, Norway); Nissen-Meyer, J. *ochim Biophys Acta* 520(1): 111-121; 1978.

Damage-dependent endonuclease activites in cell-free tracts from mouse plasmacytoma cells (line MPC-11) w characterized using ϕ x 174 RFI DNA damaged by UV l (1,000 joules/m^2), acid, or osmium tetroxide. The extract duced approx 1.1 nicks per 35 thymine-containing dimer the UV-damaged DNA. The acid-treated DNA, which c tained apurinic sites, was enzymatically broken at every kali-labile site. The extract was shown to contain an apu ic-specific endonuclease that was stimulated by magnesi stimulaton being lower for the UV-endonucleolytic acti than for the apurinic-endonucleolytic activity. Also, whe the UV-endonuclease activity was little affected by reduc the KCl concentration, the apurinic-specific activity was most completely abolished. DNA exposed to increasing c centrations of OsO_4 (to 80 μg/ml) became a progressi better substrate for the endonucleolytic activity. The respo of the OsO_4-specific endonuclease activity to KCl and Mg was qualitatively similar to that of the endonuclease acti that acted on UV-irradiated DNA. The results suggest one enzymatic activity recognized both OsO_4- and UV duced lesions in DNA (ie, pyrimidines with a saturated double bond). (24 refs)

78-6372 **Effect of DL-Tryptophan on Plastic-indu Tumorigenesis.** (Rus) Pliss, G. B. (Lab. Che cal Carcinogens, N. N. Petrov Res. Inst. Oncology, Le grad, USSR); Eliseev, V. V. *Biull Eksp Biol Med* 86 353-356; 1978.

The effect of DL-tryptophan (Try) on plastic carcinogen was studied in random-bred albino rats. A copolymer of methyl and ethyl ester of methacrylic acid was implanted in the form of a powder or plate, into the rats: 800 mg of powder was implanted into the right side and a 20- x 20 1-mm plate was implanted into the left side. On the next d the rats were divided into two groups: 34 rats in Grou received Try in sunflower oil (100 mg/day, 5x/wk, po), 32 rats in Group 2 received sunflower oil only (0.5 ml/d 5x/wk). In Group 2, the first acrylic plate-induced tum were detected 12.3 mo after transplantation: 11/27 surviv rats developed fibrosarcomas after an av latent period of mo. Implantation of the acrylic powder did not induce mors. In Group 1, the first acrylic plate-induced tumors w detected 13.8 mo after transplantation: 6/19 survivors de loped fibroblastic sarcomas (av latent period was 16.3 m Contrary to the Group 2 rats, two rats in Group 1 develop a fibrosarcoma at the site of acrylic powder implantation a 18.7 mo. (11 refs)

373 **Late Effects of Successive Massive Doses of Radiation on Parabiont Rat Pairs.** (Eng) War-
S. (Cancer Res. Inst., New England Deaconess Hosp., on, MA, 02215); Chute, R. N.; Porter, M. W.; Brown, . *Int J Radiat Biol* 34(3): 265-271; 1978.

udy was made of the life-span and leukemia and osteo- c sarcoma incidence in pairs of parabiont rats that sur- d 1,000-R doses of whole-body radiation, given first to partner and then to the other after intervals of 5, 10, and lays. The degree of recovery and of residual damage in irst irradiated rat was measured by the extent of its abili- support its subsequently exposed partner. Life-span was tened by 100-150 days following a 5-day interval and by ays following a 10-day interval, but it was not shortened wing a 30-day interval. The incidence of leukemia -7%) was the same in sequentially irradiated groups, re- lless of the time between exposures; the incidence of leu- ia in control pairs was 4.8%. Shortening the interval be- en irradiations decreased the av age at death from emia; leukemic pairs had an av age at death of 690 days those irradiated 30 days apart, 490 days for those with -day interval, and only 325 days for those with a 5-day rval. None of the pairs in which both partners were ir- ated developed solid lymphoid tumors. The incidence of ogenic sarcoma (including lesions occurring in soft parts) he parabiont pairs in which both partners were irradiated sharply increased to 12.9%, or about 8 times the rate in radiated controls (1.6%), 2 times that in pairs in a i-irradiated series (7.0%), and 9 times that in shielded tners in the hemi-irradiated series (1.4%). (14 refs)

6374 **Radiation-induced Soft-tissue and Bone Sarcoma.** (Eng) Kim, J. H. (Dept. Radiation Thera- Memorial Sloan-Kettering Cancer Center, New York, , 10021); Chu, F. C.; Woodard, H. Q.; Melamed, M. R.; vos, A.; Cantin, J. *Radiology* 129(2): 501-508; 1978.

e records of a single hospital over the past 50 yr revealed cases of soft-tissue sarcoma arising from irradiated tissues l 27 cases of radiation-induced bone sarcoma. The patients h soft-tissue sarcomas ranged in age at the time of initial tment from 7 to 44 yr, the mean and median latent period m first irradiation to the discovery of sarcoma being 12 l 16 yr, respectively. Nine of these patients were irradiated benign conditions, 10 were irradiated for malignancies, l one was occupationally exposed to radiation. The pa- nts with bone sarcomas ranged in age from 1 to 56 yr, the an and median latent period from first irradiation to the covery of sarcoma being 11 and 12 yr, respectively. Two ients were irradiated for benign conditions and 25 were adiated for malignancies. Twenty-four additional cases of liation-induced osteogenic sarcoma found in the literature embled the current patients in sex ratio, radiation dose, d induction time. The median nominal standard doses of diation associated with the soft-tissue and bone sarcomas re 1900 and 2270 rets (rads-equivalent-therapeutic), respectively. No radiation-induced tumors were seen at doses below 1100 rets. For the bone sarcomas, the latent period was longer after larger radiation doses; and children appeared to be more susceptible to the development of cancer than did adults. (30 refs)

78-6375 **Chronic Mechanical Trauma in the Aetiology of Oro-pharyngeal Carcinoma.** (Eng) Thumfart, W. (Universitats-HNO-Klinik, Waldstrasse 1, D-8520 Erlangen, W. Germany); Weidenbecher, M.; Waller, G.; Pesch, H. J. *J Maxillofac Surg* 6(3): 217-221; 1978.

The etiology of oropharyngeal carcinoma was studied in 86 patients with tumors of the oral cavity. Tumors of the gum and palate accounted for 62% of these tumors. Most (83%) of the patients were smokers and 49% regularly consumed alcohol, some to excess. In 44% of these patients, there was a coincidence of the cancer site with the site of persistent mechanical irritation by sharp teeth edges, prominent parts of an ill-fitting denture, or similar mechanical factors. Most of the tumors were keratinizing, poorly differentiated, squamous cell carcinomas, and all carcinomas in contact with a mechanical irritation had a surrounding wall of chronic inflammatory infiltration. Dysplasias of different degrees were found in the areas around the carcinomas. (16 refs)

78-6376 **Natural History of Radiation-associated Thyroid Cancer.** (Eng) Roudebush, C. P. (Thyroid Study Unit, Dept. Medicine, Univ. Chicago, Box 138, 950 E. 59th St., Chicago, IL, 60637); Asteris, G. T.; De Groot, L. J. *Arch Intern Med* 138(11): 1631-1634; 1978.

The clinical courses of 91 thyroid cancer patients who had received x-ray therapy (IR) between 1950 and 1975 were compared with those of a control group of thyroid cancer patients who had not received radiation therapy (RT). Although the two populations displayed similar profiles, several differences were apparent. In RT cases, the mean age was lower (28.2 yr vs 36.5), and, perhaps due to this, cervical adenopathy occurred more frequently (38.4% vs 25.4%). Treatment of RT patients had been more aggressive; more had total or near-total thyroidectomy (72.5% vs 56.9%) or received radioactive iodide (41.8% vs 21.9%). Primary papillary tumors were common in the RT group (87.8%). No anaplastic or medullary tumors were found, but invasive or metaplastic disease (9.9% vs 4.2%) and multifocal disease (46.5% vs 15.9%) were more prevalent in these subjects. Moreover, recurrences were more common in the RT group (6.6% vs 1.4%). The death rate was similar in both groups. Parathyroid adenomas were observed in three irradiated patients, but none occurred in the controls. (20 refs)

78-6377 **Thyroid and Parathyroid Lesions after Radiation (Letter to Editor).** (Eng) Knights, E. M.

(South Macomb Hosp., Warren, MI, 48093); Phillips, E. *Ann Intern Med* 89(5, part 1): 725-726; 1978.

A 53-yr-old woman was found to have a solitary parathyroid adenoma, a papillary adenocarcinoma of the thyroid, and a colloid nodule of the thyroid. She had been treated with radiotherapy for acne at age 18. (3 refs)

78-6378 **Radiation-induced Thyroid Carcinoma Following Treatment for Fetal Medulloblastoma.** (Pol) Borejko, J. (Klinika Radioterapii, Instytut Radiologii AM, Warsaw, Poland); Jeleniewska, A. *Pol Przegl Radiol* 42(3): 231-235; 1978.

Two patients (a girl and a boy aged 8 yr), received conventional radiotherapy for medulloblastoma. The girl received total doses of 2,500 and 2,800 R on two fields and an additional 3,300 R for a recurrence 5 yr later. She developed papillary carcinoma of the thyroid gland 16 yr after the first irradiation. The boy received a total dose of 3,500 R in 35 sessions in 67 days. He developed a mixed (papillary and follicular) thyroid carcinoma with metastases 10 yr later. (20 refs)

78-6379 **Occurrence of Previous Neck Radiotherapy among Patients with Associated Non-medullary Thyroid Carcinoma and Parathyroid Adenoma or Hyperplasia.** (Eng) Tisell, L. E. (Dept. Surgery II, Sahlgren's Hosp., S-41345 Goteborg, Sweden); Hansson, G.; Lindberg, S.; Ragnhult, I. *Acta Chir Scand* 144(1): 7-11; 1978.

The medical records of 10/16 consecutive patients (12 women, 4 men) with coexistent primary hyperparathyroidism (HPT) and nonmedullary thyroid carcinoma revealed history of prior external radiation treatment to the neck. The ages at the time of first irradiation ranged from 2 mo to 51 yr (mean, 18 yr). The time lapse between first exposure and diagnosis of HPT and thyroid carcinoma ranged from 14 to 47 yr (mean, 36 yr). The thyroid tumor was limited to the gland in eight patients (Stage I). Regional lymph node metastases without concomitant cancer growth beyond the thyroid capsule were found in six patients (Stage II). In two patients, the tumor involved adjacent structures (Stage III); one of these patients also had lymph node metastases. The thyroid carcinoma was multifocal in four patients. There were 13 patients with a single parathyroid adenoma: in 8, a rim of compressed normal parathyroid tissue was found at the periphery of the adenoma; in 3, the removed parathyroid glands showed hyperplasia. In some of the enlarged parathyroid glands, hemorrhages as well as zones of fibrosis were present. Microscopically, the enlarged parathyroids in irradiated patients were similar to those of nonirradiated patients. The results agree with the hypothesis that radiation can serve as an etiological factor in the development of associated thyroid carcinoma and HPT. (17 refs)

78-6380 **Radiation-induced Cancers in the Head Neck Region.** (Jpn) Miyahara, H. (Dept. C ryngology, Kumamoto Univ. Sch. Medicine, H Kumamoto 860, Japan); Matsuoka, H.; Ohbuchi, M.; T M.; Sato, T.; Maeda, K. *J Otolaryngol Jpn* 81(3): 233 1978.

A survey was made of 54 cases of radiation-induced c in the head and neck region. In 37 patients, the radiatio been applied as therapy for benign diseases, includin cases of tuberculous cervical lymphadenitis and 3 cas dermal disease; in 14 patients, the radiation had been to treat malignant tumors, including 9 in the larynx a in the thyroid. Among the radiation-induced cancers, were 23 hypopharyngeal tumors, 14 thyroid tumors, ar cervicoesophageal tumors. Patients irradiated for malig tumors had shorter intervals between treatment and dev ment of radiation-induced cancer (av, 9.4 yr) than pat treated for benign conditions (av, 33 yr). Most of the tu were well-differentiated squamous cell carcinomas o pharynx and larynx; there were also 14 papillary and fo lar adenocarcinomas of the thyroid gland and 1 fibrosarc of the upper lip. Studies show that the incidence of r tion-induced cancer is increasing. (16 refs)

78-6381 **Promotion of Metastasis of C3H Mouse M mary Carcinoma by Local Hyperthermia.** (Walker, A. (Glasgow Inst. Radiotherapeutics and Oncol Belvidere Hosp., London Rd., Glasgow G31 4PG, Scotla McCallum, H. M.; Wheldon, T. E.; Nias, A. H.; Abde A. S. *Br J Cancer* 38(4): 561-563; 1978.

The response to hyperthermia of an infrequently metast ing transplantable mammary carcinoma that originally a spontaneously in C3H mice was investigated. Using a w heater that transfers heat via a thin membrane, heat was plied to 5- to 7-mm dorsal tumors in a temperature rang 42-46 C and a time range of 1-2 hr, time-temperature cor nation sufficient to eradicate the primary tumor. Fifty- mice had their tumors locally controlled at 100 days o time of death or sacrifice, if earlier. Of these mice, 7 unexpectedly prior to routine autopsy and 14 were autop because of unexpected early death or physical deteriorat All 14 autopsied mice were found to have pulmonary me tases and, in some cases, metastases at other sites (4 to kidney, 3 to brown fat, and 1 each to heart, diaphra spleen, and lymph node). Taking only the proved metasta the minimum rate for metastasis in this group was 14/ which may be contrasted to the max rate found previo in 14/131 mice whose tumors were locally controlled radiation. (11 refs)

78-6382 **Tumors in Animals Irradiated During Embr genesis.** (Rus) Strel'tsova, V. N. (No affiliat given); Pavlenko-Mikhailov, Iu. N. *Vopr Onkol* 24(9): 25- 1978.

effect of irradiation during embryogenesis on tumor de-
pment was studied in male and female white rats whose
hers were irradiated with a single ^{60}Co dose of 100 rads
se rate, 168 rads/min) on gestation days 7, 14, or 19. The
animals that died at age 200-600 days were evaluated.
tumor induction rate was 184/219 vs 9/53 controls. The
ors included 52 breast tumors, 42 cases of leukemia, 53
ophyseal tumors, 11 ovarian tumors, 4 adrenal tumors,
hyroid tumors, 3 lung tumors, 3 bone tumors, and 1 tu-
r of the skin, uterus and intestine. The tumor incidence
t occurred after irradiation during the embryonal (day 7)
fetal (day 19) periods was 69/107 and 44/70, respective-
Eighteen of the 42 animals irradiated during organogene-
(day 14) developed tumors by day 400, but animals ir-
iated during the embryonal and fetal periods developed
ors by days 120-180. The incidence of new tumors was
hest during the last third of the life-span. Male rats ir-
iated during embryogenesis developed mammary gland
bone tumors, and females developed ovarian and bone
ors; these tumors were not seen in the controls. (12 refs)

6383 **Bilateral Pleural Thickening: A Manifestation of Asbestos Dust Exposure.** (Eng) Sargent, E. (Dept. Radiology, Los Angeles County-Univ. Southern ifornia Medical Center, 1200 N. State St., Los Angeles, , 90033); Gordonson, J.; Jacobson, G.; Birnbaum, W.; ub, M. *Am J Roentgenol* 131(4): 579-585; 1978.

irty-six asymptomatic patients with radiologic evidence of ural thickening were discovered to have been occupation- exposed to asbestos dust, although this fact was clinically suspected. Pleural thickening most frequently involved d was max at the level of the fifth through eighth ribs and erspaces. There was no associated involvement of the ces of the lung or the costophrenic angles. Most (67%) the patients showed thickening up to 5 mm wide, and 8% owed thickening > 10 mm wide. The extent and severity he pleural thickening did not correlate with the total dura- n of or time elapsed since asbestos exposure. Pleural thick- ng or plaques with no other evidence of disease in a rela- ely asymptomatic patient is a sign of possible exposure to estos dust. When retrospectively correlated with a lifetime cupational history, bilateral pleural thickening might serve an indicator of asbestos dust exposure in the general popu- ion. (23 refs)

-6384 **Renal Cell Carcinoma Following Radiation Therapy for an Adrenal Cortical Carcinoma.** ng) Andler, W. (Dept. Pediatrics, Univ. Essen, Hufe- idstr. 55, D-4300 Essen 1, W. Germany); Havers, W.; mbolis, C.; Medrano, J.; Stollmann, B. *J Pediatr* 93(4): 4-636; 1978.

The occurrence of renal cell carcinoma in an 11-yr-old girl approx 10 yr after radiation therapy for an adrenal cortical carcinoma is reported. The renal cell carcinoma was in all likelihood a direct consequence of the radiation therapy. (10 refs)

78-6385 **Influence of Misonidazole on the Incidence of Radiation-Induced Intestinal Tumours in Mice.** (Eng) Rostom, A. Y. (Regional Centre Radiotherapy and Oncology, St. Lukes Hosp., Warren Road, Guildford, Surrey GU1 3NT, England); Kauffman, S. L.; Steel, G. G. *Br J Cancer* 38(4): 530-536; 1978.

The combined effects of misonidazole (MSD: 1 mg/g ip) and abdominal radiation in the range 16-24 Gray (Gy) units (1 unit = 100 rads) were studied in male C57BL mice. Eighty-one of 105 mice given radiation alone survived 50 days or longer, as did 81/106 mice sensitized with MSD 45 min before irradiation. Although the proportion of mice developing intestinal adenocarcinomas was similar in the two groups (60% and 68%, respectively) the incidence of multiple tumors was significantly higher in the MSD group (41% vs 18%). The av number of tumors per mouse was higher in the MSD groups at every radiation level, but the difference in the MSD and irradiation-only groups was most marked at a 20 Gy dose. With radiation alone, the most common tumor site was the cecum (49% of tumors) followed by the rectum (27%). MSD treatment reduced the cecal tumor incidence (37%), but it increased the rectal tumor incidence (40%). Most of the adenocarcinomas were mucin-secreting and located in regions of radiation damage. Although MSD may sensitize normal intestinal cells to the carcinogenic effect of radiation, these results do not call into question its present clinical use. However, there is the possibility that chemical radiosensitizers could enhance the incidence of second cancers in patients responding to radiotherapy. (15 refs)

78-6386 **Scenarios of ^{14}C Releases from the World Nuclear Power Industry from 1975 to 2020 and the Estimated Radiological Impact.** (Eng) Killough, G. G. (Health and Safety Res. Div., Oak Ridge Natl. Lab., Oak Ridge, TN); Till, J. E. *Nucl Saf* 19(5): 602-617; 1978.

Radioactive ^{14}C is formed as a by-product of nuclear power generation and a part is released to the environment. Estimated releases of ^{14}C from presently operating nuclear power facilities are still quite small in comparison with natural and other man-made sources, but potential growth in world demand for power will raise the quantity produced and released. The radiation dose to world population from natural and man-made ^{14}C is calculated based on three possible scenarios: (1) A pessimistic scenario (P) in which all the ^{14}C projected to be produced in fuel cycles is released. (2) An optimistic scenario (O) that assumes a decontamination fac-

tor of 100 for fuel reprocessing. (3) An intermediate scenario (I) that simulates a phased improvement in effluent treatment technology. The P scenario projects a ^{14}C release rate by the nuclear industry that exceeds natural production after the year 2000. The O and I scenarios project that ^{14}C release from the nuclear industry would attain a stationary level at approx 37% of natural production by 2020. Potential effects on the incidence of cancers and genetic disorders are calculated for the three scenarios from risk factors for exposure to ionizing radiation and ^{14}C specifically estimated by the International Commission on Radiological Protection. Total number of cancers and genetic effects over infinite time (effectively 46,000 yr or about eight half-lives of ^{14}C) are given for each of the three scenarios. For the O and I scenarios the cumulative potential health effects are about 22% of those from natural ^{14}C formed from 1975-2020, about 6% of those from weapons testing, and $<0.04\%$ of those from natural already in the environment. (45 refs)

See also:
*(Rev.): 78-6004, 78-6008, 78-6025, 78-6031, 78-60
78-6045, 78-6046, 78-6047, 78-6048, 78-60
78-6051, 78-6052, 78-6055.
*(Chem.): 78-6108, 78-6111, 78-6120, 78-61
78-6154, 78-6196, 78-6235, 78-62
78-6244, 78-6313, 78-6325, 78-63
*(Immun.): 78-6490.
*(Path.): 78-6509, 78-6512, 78-6516, 78-65
78-6529.
*(Epid.-Biom.): 78-6547, 78-6554, 78-6564, 78-65

-6387 **Identification of Nucleotide Sequences Which May Encode the Oncogenic Capacity of Avian etrovirus MC29.** (Eng) Sheiness, D. (Dept. Microbiology, niv. California, San Francisco, CA, 94143); Fanshier, L.; shop, J. M. *J Virol* 28(2): 600-610; 1978.

ıe genome of MC29 virus, a retrovirus that induces a varie- of tumors in chickens (ie, myelocytomatosis, kidney and er carcinomas), and transforms cultures of embryonic avi- macrophages and fibroblasts, was characterized, and nu- eotide sequences that may encode the oncogenic potential the virus were identified. MC29 virus can replicate only ith the assistance of a related helper virus (MCAV), and e replication defect is apparently due to a deletion in one more viral genes. The haploid genome of MC29 virus has mol wt of approx 1.7 x 10^6, whereas the MCAV genome ıs a mol wt of 3.1 x 10^6. Although MC29 virus transforms ian fibroblasts in culture, its genome does not contain a ene homologous to the *src* gene responsible for fibroblast ansformation by avian sarcoma viruses (ASV's). Radioac- ve DNA complementary to nucleotide sequences found in ıe MC29 virus genome (cDNA-MC29), but not in that of ICAV, were prepared. Hybridization data showed that the IC29 virus genome contained approx 1,500 nucleotides not ound in MCAV, ASV, or Rous-associated virus 0, an en- ogenous virus of chickens. These sequences could encode art or all of the gene(s) responsible for MC29 virus onco- enesis and transformation. The use of cDNA-MC29 will elp determine the evolution of MC29 and may assist in iden- fying its transforming functions and in relating these func- ons to those of other leukosis-leukemia viruses. (43 refs)

8-6388 **OK 10 Virus, an Avian Retrovirus Resembling the Acute Leukaemia Viruses.** (Eng) ker-Blom, N. (Dept. Virology, Univ. Helsinki and Coll. eterinary Medicine, Helsinki, Finland); Hortling, L.; allio, A.; Nurmiaho, E. L.; Westermarck, H. *J Gen Virol* 0(3): 623-633; 1978.

he isolation and characterization of the OK 10 virus com- lex, which was derived from a liver tumor in a chicken that ad been inoculated iv as an embryo with a field isolate of n avian leukosis virus, are described. Interference assays in- icated that this virus complex contained both transforming OK 10 V) and nontransforming (OK 10 AV) virus, both of ubgroup A. OK 10 V, which could not be isolated in vitro ithout OK 10 AV, induced foci in chick embryo cells under gar overlay, and the cells from these foci formed colonies ı soft agar. Injection of virus or infected cells into chicks esulted in acute leukemia but no local tumors. OK 10 AV, hich comprised about 99% of the OK 10 complex, did not induce foci in chick embryo cells, but it caused leukosis in chickens 17 mo after injection. OK 10 stocks showed typical C-type virus particles that had a density of 1.16 g/ml and contained 70S RNA. The latter released type b RNA subunits after heat denaturation. The data indicate that OK 10 virus is related to the subgroup C MH 2 virus or to the acute leukemia viruses of chickens. (33 refs)

78-6389 **Rapid Oncogenesis In Vivo by Chicken Retrovirus OK10.** (Eng) Hortling, L. (Dept. Virology, Univ. Helsinki, Haartmaninkatu 3, SF-00290 Helsinki 29, Finland). *Acta Pathol Microbiol Scand (B)* 86(4): 185-192; 1978.

The pathogenesis of OK10 virus infection was studied in 2- to 4-day-old Brown Leghorn chickens injected intraabdominally with 0.5 ml OK10 virus stock (titer: 5 x 10^4 focus-forming units/ml). The associated virus OK10AV was detected after 1 wk in the bursa of Fabricius, thymus, and liver, but not in spleen and bone marrow. OK10AV was detected in the spleen 3 wk after infection. The transforming virus OK10V was detected only in the bursa of Fabricius 2 wk after infection and in all tissues tested except bone marrow 3 wk after infection. Neutralizing serum antibodies against the OK10 virus complex were detected after 3 wk, when the first tumor was seen in the gut mesentery. After 6 wk, tumors were found in the liver but not in any other organs. When chickens were injected iv with OK10 virus, tumors could also be detected in the liver, kidneys, and testes. The mesenteric tumors were composed of two kinds of cells: clear cells with a large nucleus, prominent nucleoli, and cytoplasmic vacuolation and surrounding lymphocytes. OK10AV was infectious for chickens and induced neutralizing serum antibodies. One of seven chickens infected with OK10AV died of leukosis after 1.5 yr. Continuous cell lines, established from OK10 virus-induced tumors, produced both OK10V and OK10AV viruses and had a blastlike morphology. It is concluded that the OK10 virus complex, composed of a very oncogenic virus OK10V and an associated weakly oncogenic virus OK10AV, may be a good model for studying the mechanism of oncogenesis in vivo and in vitro. (33 refs)

78-6390 **Temperature-sensitive Mutant of Avian Erythroblastosis Virus Suggests a Block of Differentiation as Mechanism of Leukaemogenesis.** (Eng) Graf, T. (Institut fur Virusforschung, Deutsches Krebsforschungszentrum, im Neuenheimer Feld 280, D-6900 Heidelberg, W. Germany); Ade, N.; Beug, H. *Nature* 275(5680): 496-501; 1978.

Virus-induced leukemic transformation was investigated by isolating a temperature-sensitive (*ts*) mutant of avian erythroblastosis virus (AEV). Erythroblast (EB) colonies were produced by infecting bone marrow cultures with mutagen-treated AEV at 35 C and seeding them into semisolid medium. Cells from individual colonies were propagated at 35 C. Aliquots of these clones were then shifted to 41 C or kept at 35 C and assayed for benzidine-positive (B+) cells. Three clones were *ts* for Hb expression, containing > 70% strongly B+ cells at 41 C and < 10% at 35 C. Clone 34 produced virus (*ts*34 AEV) capable of inducing EB colonies *ts* for Hb expression. *ts*34 AEV (1,000 colony-forming units) was less leukemogenic than the parent virus (10 units) in 8-day-old chicks: there was a decreased incidence of animals that died of leukemia and a delay of onset of disease and death. Most of the leukemic EB's from the peripheral blood of the mutant-infected chicks exhibited *ts* properties. It is suggested that AEV induces a block of differentiation in the erythroid target cells, that this block plays a crucial part in virus-induced leukemogenesis, and that the continuous expression of viral gene product is necessary to maintain the leukemic state of infected cells. (18 refs)

78-6391 **At Least 104 Nucleotides Are Transposed from the 5′ Terminus of the Avian Sarcoma Virus Genome to the 5′ Termini of Smaller Viral mRNAs.** (Eng) Cordell, B. (Dept. Biochemistry and Biophysics, Univ. California, San Francisco, CA, 94143); Weiss, S. R.; Varmus, H. E.; Bishop, J. M. *Cell* 15(1): 79-91; 1978.

Based on the previous finding that all three forms of avian sarcoma virus (ASV)-specific cytoplasmic RNA contain a nucleotide sequence that is homologous to a sequence of 101 contiguous nucleotides found at the 5′ terminus of the ASV genome, but not within the 3′ half of the genome, it was proposed that this nucleotide sequence may be transposed to the 5′ termini of viral messenger RNA's (mRNA's) during the genesis of these RNA's. Two strategies were used to substantiate this proposal. First, the three forms of ASV mRNA were isolated by molecular hybridization. Chemical analysis was then used to demonstrate that all three forms shared a capped nucleotide sequence from the 5′ terminus of the viral genome, although other portions of the 5′ half of the genome were not present in the smaller viral mRNA's. Second, single-stranded DNA complementary to a sequence of 101 nucleotides at the 5′ terminus of the ASV genome (cDNA-5′) was prepared, and it was shown that all three forms of ASV mRNA could form RNAase-resistant duplexes with the full extent of cDNA-5′. The RNA sequences included in these duplexes were capped and had identical compositions. In contrast, fragments of RNA derived from the 3′ half of the ASV genome did not form duplexes with cDNA5′. It is concluded that a sequence of > 100 contiguous nucleotides is transposed from the 5′ terminus of the ASV genome to the 5′ termini of smaller virus-specific RNA's during the genesis of these RNA's. (53 refs)

78-6392 **Nucleotide Sequences Related to the Tra forming Gene of Avian Sarcoma Virus Are P sent in DNA of Uninfected Vertebrates.** (Eng) Spector, H. (Dept. Microbiology, Univ. California, San Francis CA, 94143); Varmus, H. E.; Bishop, J. M. *Proc Natl A Sci USA* 75(9): 4102-4106; 1978.

Purified radioactive DNA complementary to the avian s coma virus (ASV) transforming gene (cDNA-sarc) was nealed with the DNA of several uninfected species under c ditions conducive to pairing of partially matched nucleot sequences (1.5 M NaCl, 59 C). Denatured DNA's of 10- 11-day-old chicken embryos, liver and spleen of a GR mou human placental tissue, calf thymus, salmon sperm, sea chin sperm, *Drosophila* cells grown in culture, *Escheric coli* cells, and XC cells from a tumor in an ASV-infected were incubated for 96-120 hr with ^{3}H-cDNA-sarc. Dup formation was measured by hydroxyapatite fractionati cDNA-sarc formed duplexes with mammalian and f DNA's (18%-43%), chicken DNA (55%-62%), and XC DNA (65%), but only slight annealing occurred with urchin DNA and none occurred with *E. coli* or *Drosoph* DNA. Kinetics studies indicated that the nucleotide quences related to cDNA-sarc in species in which anneal occurred were present as single or only a few copies. T failure of total hybridization in these species was most pro bly due to stoichiometric limitations imposed by mismatch base pairs and not due to insufficient amounts of cDNA. T degree of base mismatching, as determined by the therm stability of the duplexes, was approx 3%-4% for chick DNA and 8%-10% for mammalian or fish DNA. These sults indicate that there is a highly conserved set of nucleot sequences to at least a portion of the ASV sarc gene in t DNA of these vertebrates. (29 refs)

78-6393 **Specific Restriction of Avian Sarcoma Virus by a Line of Transformed Lymphoid Cel** (Eng) Neiman, P. E. (Dept. Medicine, Div. Oncology, Un Washington, Seattle, WA, 98195); McMillin-Helsel, Cooper, G. M. *Virology* 89(2): 360-371; 1978.

The properties of viral replication on MSB-1 cells, a line transformed chicken lymphoid cells derived from tumors duced by Marek's disease viruses, were examined. These ce are susceptible to infection by avian leukosis virus (ALV) subgroups A and C, including transformation-defective (deletion mutants of avian sarcoma virus (ASV). Vario parameters of viral growth revealed that infection of MSB cells by *td* ASV was indistinguishable from infection of chic en embryo fibroblasts (CEF) by *td* ASV. However, t growth of wild-type ASV was restricted in these cells. Furth studies, employing Hirt supernatant fractionation, suggest that, following infection of MSB-1 cells with ASV, infectio proviral sequences were synthesized, but the viral DNA d not integrate into host cell DNA in a normal fashion and w lost from the cell. Since replication of *td* ASV does not see to be restricted in MSB-1 cells, it is concluded that the failu

SV DNA to integrate normally in these cells is due to presence of *src* sequences (genes that confer the ability ansform CEF and other cell types) in the viral genome. refs)

394 **Effect of Glucosamine on Virus Production and Antigen Expression in Avian Sarcoma s-transformed Cells.** (Eng) Israel, E. (Departement de robiologie et d'Immunologie, Universite de Montreal, ntreal, Quebec, Canada); Mandeville, R.; Wainberg, M. *Can J Microbiol* 24(9): 1024-1031; 1978.

effect of glucosamine (20 mM) on virus production and gen expression in chicken embryo fibroblast (CEF) cells sformed by avian sarcoma virus was studied. Significant ntities of transforming virus were not synthesized by cells osed to glucosamine, and glucosamine significantly inhib- viral RNA synthesis and the levels of RNA-dependent A polymerase. The inhibition was reduced when glucosa- e treatment was carried out in the presence of glucose. cosamine treatment also affected antigenic expression in sformed CEF, as measured by an indirect immuno- rescence test, but the degree of inhibition was far less en a lymphocyte-stimulation assay for the detection of -mediated immunity was used. (22 refs)

6395 **Synergistic Effect of Tumor Virus Transformation and Tumor Promoter Treatment on the duction of Plasminogen Activation by Chick Embryo Fiblasts.** (Eng) Goldfarb, R. H. (Dept. Microbiology and munology, State Univ. New York, Downstate Medical nter, Brooklyn, NY, 11203); Quigley, J. P. *Cancer Res* 12): 4601-4609; 1978.

dies were carried out to determine whether the tumor pro- ter phorbol myristate acetate (PMA) could further en- nce the protease plasminogen activator (PA) activity in tures of chick embryo fibroblasts transformed by Rous coma virus (RSVCEF). PMA caused a 12- to 13-fold en- ncement of the extracellular PA activity in these cultures, ich in the absence of PMA produced at least 50- to)-fold more PA than did normal chick embryo fibroblasts. e increase in RSVCEF PA activity was first detectable at 'MA concentration of 1 nanogram (ng)/ml, but was max en the PMA concentration was between 25 and 100 /ml. Increased levels of PA activity in RSVCEF were ob- ved as early as 1-2 hr after PMA treatment. Sodium dode- sulfate-polyacrylamide gel electrophoresis demonstrated t the PA produced by PMA-treated cultures had a mol identical to that of the PA produced by untreated cultures. induction by PMA could not be accomplished in cell-free racts, but required protein synthesis in intact cells. Under um-free conditions, PMA-treated RSVCEF secreted high els of PA for 4-6 days and underwent pronounced mor- ological alterations; large dense colonies of round, refrac- tile cells formed, and it appeared that at least 80%-90% of the cells in the culture dish were in colonial aggregates. Modified culture conditions and the use of PMA to induce PA allowed the accumulation of large amounts of RSVCEF culture fluid and subsequent purification of the enzyme. The sensitivity of transformed chick embryo fibroblasts to PMA and the generation of enhanced proteolytic activity in the cellular microenvironment may provide a model system to examine the role of both PA in malignant transformation and PMA in tumor promotion. (68 refs)

78-6396 **Reversion of Transformed Glycolysis to Normal by Inhibition of Protein Synthesis in Rat Kidney Cells Infected with Temperature-sensitive Mutant of Rous Sarcoma Virus.** (Eng) Carroll, R. C. (Dept. Biology, Univ. California at San Diego, La Jolla, CA, 92093); Ash, J. F.; Vogt, P. K.; Singer, S. J. *Proc Natl Acad Sci USA* 75(10): 5015-5019; 1978.

Normal rat kidney cells infected with a temperature-sensitive mutant (LA23) of Rous sarcoma virus exhibit the transformed phenotype when grown at the permissive temperature (33 C) and the normal phenotype when grown at the nonpermissive temperature (39 C). Since the addition of protein synthesis inhibitors to infected cells at the lower temperature causes them to revert to the normal phenotype with respect to morphological and cytoskeletal characteristics, studies were carried out to determine if there is also a reversion in metabolic characteristics. Two sets of experiments, performed at widely separated times, gave qualitatively similar but quantitatively different results. In the first experiments, lactate production was 50%-60% greater in LA23-infected cells at the permissive temperature than in those at the nonpermissive temperature; in the other experiments, the corresponding difference was 80%-100%. In both experiments, all cells showed an increased rate of glycolysis when dinitrophenol was added to the assay, and the control rate/dinitrophenol rate ratio was greater for the transformed phenotype than for normal. In the first experiment, oligomycin inhibited the glycolytic rate of LA23-infected cells at the permissive temperature by more than 70%, but it had no effect in cells grown at the nonpermissive temperature. The glycolytic rate in the transformed cells was unchanged by oligomycin in the second set of experiments, but the drug reproducibly increased the glycolytic rate by about 20% in cells exhibiting the normal phenotype. When transformed cells grown at the 33 C were treated with cycloheximide (15 ng/ml) or abrin (200 ng/ml), the rate of glycolysis without any other additives decreased to normal values. In the first set of experiments, cycloheximide treatment also caused a return to normal of the control rate/dinitrophenol rate ratio and eliminated the oligomycin sensitivity of the rate. Other metabolic changes that might be correlated with transformation were investigated in the second set of experiments: glucose transport, hexokinase activity, and phosphofructokinase activities. The results support the thesis that transformation by the *src* gene of the Rous sarcoma virus is a pleiotypic and

reversible process, such as that involved in a pleiotypic enzymatic modification reaction and its reversal. (31 refs)

78-6397 **The Expression of Plasminogen Activator in Rous Sarcoma Virus-transformed Cells Is Controlled Both by the Virus and the Cell.** (Eng) Wolf, B. A. (Rockefeller Univ., New York, NY, 10021); Goldberg, A. R. *Virology* 89(2): 570-577; 1978.

The ability of virus produced by clones of Rous sarcoma virus (RSV)-transformed chicken embryo fibroblasts to elevate the level of cellular plasminogen activator (PA) was analyzed by a casein-plaque assay. The genotype of the virus produced by these transformed clones, which exhibit variable low to high levels of PA, was found to be identical to that of the parent virus, regardless of the PA level of the cell in which the virus is replicated. Virus from low PA clones was not defective in its ability to produce transformed cells with increased levels of PA. This virus produced the same spectrum of plaque-forming foci and soft-agar clones as virus from intermediate or high PA clones. These findings lead to the conclusion that the level of PA is cellularly determined. Additional evidence, however, such as the increased expression of PA by superinfection of low activator clones with another strain of RSV, the ability of some RSV strains to elevate PA levels, and the ability of cells infected with some temperature-sensitive *src* mutants to express properties of transformed cells at nonpermissive temperatures, suggests that PA levels are also influenced by the *src* (transforming) gene of RSV. (33 refs)

78-6398 **Lack of Correlation Between Tumorigenicity and Level of Plasminogen Activator in Fibroblasts Transformed by Rous Sarcoma Virus.** (Eng) Wolf, B. A. (Rockefeller Univ., New York, NY, 10021); Goldberg, A. R. *Proc Natl Acad Sci USA* 75(10): 4967-4971; 1978.

The oncogenicity of chick embryo fibroblast (CEF) clones derived from infection with the replication-defective Bryan strain of Rous sarcoma virus (RSV) was studied to determine whether there is a correlation between tumorigenicity and the level of plasminogen activator (PA) in transformed fibroblasts. CEF clones transformed by B77 and Prague strains of RSV, previously isolated from agar suspension culture, varied in the expression of PA activity, but the tumorigenicity of the transformed cells could not be evaluated with clone cells because B77 and Prague RSV replicate and cause sarcoma in chickens. The range of properties exhibited by the Bryan RSV-derived clones fell within the continuum observed for the B77 and Prague clones. Thus, all clones exhibited an altered (round) morphology, a two- to fivefold greater rate of sugar transport, and a 10^5- to 10^6-fold higher efficiency of growth in agar suspension, regardless of the PA level. Five clones, transformed by the Bryan strain and showing low, intermediate, or high PA activity, were tested for tumorigenicity in newborn chicks. The three clones with low activity exhibited little caseinolysis relative to the clone the highest activity, even though 3-4 times more cells assayed. At both cell concentrations tested (500 and 5 cells/chick), all clones induced tumors at the two site injection. Latency periods were similar, regardless of the tivator level of the clone injected. Every injected clone gardless of its activator activity prior to injection, indu tumors exhibiting a spectrum of plasminogen activator ac ty. No correlations could be made with regard to the of PA, size of excised tumor, number of cells surviving plantation, or morphology of explanted tumors. These re confirm previous conclusions that tumorigenicity is not related with the level of plasminogen activator. (42 refs

78-6399 **Heterogeneity of RNA Synthesized in Lys of Rous Sarcoma Virus Particles.** (Rus) P vozchikov, A. P. (N. N. Petrov Oncologic Res. Inst., Le grad, USSR); Ratovitskii, E. A.; Korobitsyn, L. P.; Knia P. G.; Seits, I. F. *Dokl Akad Nauk SSSR* 241(3): 714- 1978.

The RNA polymerase of lysates of Rous sarcoma virus (R particles was reacted with ^{3}H- or ^{32}P-labeled ribonucleo triphosphates, and the product was characterized. The s thesis product was found to be sensitive to RNAse A KOH, but less sensitive to DNAse. Electrophoresis in 2. polyacrylamide gels revealed two radioactivity peaks at and 18S-20S; there was a shift toward 4S with increas reaction time, which may indicate the presence of endogen RNAse activity. Synthesis of heteropolynucleotides was served in the lysates in the presence of all four ribonucleos triphosphates. Hybridization of the ^{3}H-labeled product of RNA polymerase reaction, isolated from the RSV lysa with RSV RNA demonstrated that 16% of the ^{3}H-labe product has complementary segments with the virion RN Thus, the lysates of RSV particles contain an RNA polyn rase that catalyzes the synthesis of both homo- a heteropolyribonucleotides, and the synthesis of at least p of the RNA is a matrix reaction, with the matrix being RSV RNA. This fact is of particular interest in light of generally held view that only RNA-dependent DNA polyn rase activity is present in oncornaviruses. (10 refs)

78-6400 **Complementary Interaction Between Gene and Immunologic Mechanisms in Determini Induction of Tumors by Rous Sarcoma Virus on the Cho oallantoic Membrane of the Chick Embryo.** (Eng) Bower, K. (Dept. Botany, Univ. Arkansas at Fayetteville, Fayet ville, AR, 72701); Gyles, N. R. *In: Prevention and Detecti of Cancer. Proceedings of the Third International Symposiu on Detection and Prevention of Cancer Held by the Intern tional Study Group for the Detection and Prevention of Can in New York, April 26 - May 1, 1976.* International Stu Group for the Detection and Prevention of Cancer. (Ne York, NY): Vol. 2(part 1), 2404 pp.; 1645-1658; 1978.

idies were conducted to determine whether the genetic chanism for regression has any influence on the number tumors on the chorioallantoic membranes (CAM) of chick bryos and on the regression of tumors induced in young cks by Rous sarcoma virus (RSV). CAM from 322 chick bryos originating from matings between parents of the rebred Progression and Regression lines were examined. ick embryos descended from unchallenged regressor (R) rents and from progressor (P) parents were equally susceple to induction of tumors on CAM by RSV. Chick embryos m immune R parents and those from a parental mating which only the dam was an immune R demonstrated a rked reduction in tumor counts compared with embryos P parents. The data suggest that a maternal factor transtted from the immune hen through the egg interacts with e genotype of the embryo to reduce the number of CAM nors. Three hundred and forty-four chicks, with parents m the same three breeding groups as those used for the AM study, were injected in the wing web with RSV at age day, 2 wk, and 4 wk. Day-old chicks descended from imne R parents demonstrated the greatest ability to effect nor regression compared with chicks from all other mating mbinations. This result also demonstrates the importance an interaction between the material factor from immune ns and the genotype of the newly hatched chick in facilitatg tumor regression. The influence of the maternal factor minished sharply at 2 wk of age and was not detectable at wk. (16 refs)

-6401 **Processing of 60,000-Dalton *sarc* Gene Protein Synthesized by Cell-Free Translation.** (Eng) amine, J. (Dept. Biology, Massachusetts Inst. Technology, ambridge, MA, 02139); Buchanan, J. M. *Proc Natl cad Sci USA* 75(9): 4399-4403; 1978.

ew Zealand White rabbit antiserum directed against the),000-dalton (60K) transformation-specific antigen of chmidt-Ruppin subgroup D Rous sarcoma virus RD-RSV) immunoprecipitated both the 60K and 25K ansformation-specific proteins synthesized by cell-free tranation of virion RNA. However, upon incubation of the anserum with ^{35}S-methionine-labeled protein from RD-RSV-infected cells, a 25K protein and one that was apox 2K smaller than 60K were immunoprecipitated, which ggests that the primary translation product is processed tracellularly. Peptide mapping of sodium dodecyl sulfate/olyacrylamide gels indicated that the 60K translation prodct and the 60K cellular protein are closely related structurly. Addition of canine pancreas membrane vesicles to the ticulocyte lysate system during cell-free translation of ansforming (*sarc*) gene messenger RNA specifically cleaved 2K segment from the 60K protein so that it comigrated with e cellular species. Secretory proteins and, probably, at least me integral membrane proteins were synthesized with ort hydrophobic signal sequences at their NH_2 terminus. he segment lost from the 60K transformation-specific proin is suggested to be a signal sequence, as the membrane vesicles processed the 60K protein only during translation and the processed protein was sequestered by the vesicles. It is concluded that the 60K *sarc* protein is synthesized as a precursor with a signal sequence that functions to insert or transport the processed protein into or through cellular membranes. (28 refs)

78-6402 **Reversion of Temperature Sensitive Transformation Mutants of Rous Sarcoma Virus and its Effect on the Expression of Tumour Specific Surface Antigen.** (Eng) Wyke, J. A. (Imperial Cancer Research Fund, P.O. Box 123, Lincoln's Inn Fields, London WC2A 2PX, England); Kurth, R. *J Gen Virol* 40(3): 701-704; 1978.

To determine whether transformation and the expression of tumor-specific cell-surface antigen (TSSA) are causally related, reversion for TSSA expression was studied in the Rous sarcoma virus mutants *tsLA29* and *tsLA33*, which show a temperature-sensitive (*ts*) expression of TSSA, and their wild-type revertants. Chick embryo fibroblasts infected with *ts* virus showed low TSSA expression at the restrictive temperature (41 C), but cells infected by the two revertants expressed TSSA levels at this temperature comparable to those expressed at the permissive temperature (35 C). The revertants were all wild-type for transformation, as judged by focus formation and sugar transport, and they all showed a wild-type expression of TSSA. The results indicate that it is extremely unlikely that TSSA expression and transformation are unrelated, and they suggest that TSSA is necessary and sufficient for transformation or that TSSA expression is concomitant with but insufficient to account for the appearance of other parameters of transformation. (15 refs)

78-6403 **Mechanism of Transfection of Chicken Embryo Fibroblasts by Rous Sarcoma Virus DNA.** (Eng) Cooper, G. M. (Sidney Farber Cancer Inst., Boston, MA, 02115); Okenquist, S. *J Virol* 28(1): 45-52; 1978.

The mechanism of transfection of chicken embryo fibroblasts (CEF) by Rous sarcoma virus (RSV) DNA was investigated by assaying DNA-mediated transformation under conditions that restrict secondary virus infection (SVI). CEF that were genetically resistant to virus infection as a result of the absence of receptors for virus penetration were also resistant to transformation by integrated or unintegrated RSV DNA, as assayed by focus formation. Since resistance to RSV infection appears to be expressed at the level of virus penetration, these results indicate that focus formation by RSV DNA required formation of extracellular progeny virus and SVI of sensitive cells. DNA of replication-defective Bryan high-titer RSV was noninfectious, and transformation by DNA of a temperature-sensitive (ts) DNA polymerase mutant was ts. These results indicate that SVI was necessary for transformation by RSV DNA. Since transformation was also assayed by colony formation in soft agar, the requirement for SVI was not an

artifact of possible difficulties in detecting foci formed only by cell division. Thus, exposure to RSV DNA did not result in genetically stable transformation of the primary DNA-treated recipient cells. The results are consistent with the hypothesis that transfection of CEF by RSV DNA proceeded by transcription of donor DNA, formation of extracellular progeny virus, and SVI of sensitive cells. (30 refs)

78-6404 **Transfer of Duck Cell DNA Sequences to the Nucleus of 3T3 Cells by Rous Sarcoma Virus.** (Eng) Baxt, W. G. (Biology Dept., Univ. California at San Diego, La Jolla, CA, 92037); Meinkoth, J. L. *Proc Natl Acad Sci USA* 75(9): 4252-4256; 1978.

The ability of a retrovirus [Prague C Rous sarcoma virus (RSV)] to transduce incorporated host polynucleotide sequences into the nucleus of a second unrelated host cell was studied. Upon infection of Peking duck cells by Prague C RSV, polynucleotide sequences complementary to Peking duck cell nuclear DNA were detected in the high-mol-wt RNA from progeny Peking duck cell-passaged RSV (RSV-PD) by RNA-DNA hybridization. When mouse 3T3 cells were subsequently infected by RSV-PD, polynucleotide sequences complementary to Peking duck cell nuclear DNA were detected in the 3T3 cell nuclear DNA by RNA-DNA molecular hybridization. The data introduce the possibility that passage of intact genes or portions of genes between species might occur after evolutionary divergence has taken place. In this manner, the gene composition of organisms could undergo modulation at a rate considerably greater than the one that would result from random mutations alone. (38 refs)

78-6405 **Isolation and Characterization of a Virus-specific Ribonucleoprotein Complex from Reticuloendotheliosis Virus-transformed Chicken Bone Marrow Cells.** (Eng) Wong, T. C. (Dept. Microbiology, Univ. Texas Health Science Center at Dallas, Southwestern Medical Sch., Dallas, TX, 75235); Kang, C. Y. *J Virol* 28(1): 34-44; 1978.

A ribonucleoprotein (RNP) complex containing endogenous RNA-directed DNA polymerase (RDDP) activity was isolated from the cytoplasm of reticuloendotheliosis virus (REV)-transformed chicken bone marrow cells (BMC) but not from normal BMC. This RNP complex has a density of 1.23 g/cm^3 and sediments at 80S-100S in sucrose gradients, properties that indicate that it is distinct from the mature virion. RDDP activity was completely neutralized by anti-REV DNA polymerase antibody but not by anti-avian myeloblastosis virus DNA polymerase antibody. The DNA product from the endogenous RDDP reaction of the RNP complex hybridized to REV RNA but not to avian leukosis virus RNA. The RNA extracted from the RNP hybridized only to REV-specific complementary DNA (cDNA) synthesized from an endogenous DNA polymerase reaction of p fied REV. Max hybridization was only 40%; the significa of this apparently low hybridization efficiency is not cl The size of the RNA in the RNP is 30S-35S, a size equiva to one subunit of the RNA genome of the virus. No mature genomic RNA was found within the RNP comp Thus, the formation of mature viral genomic RNA seem occur after budding, probably during the condensation of nucleoid. (32 refs)

78-6406 **Protection Against Marek's Disease-deri Tumor Transplants by the Nononcogenic S Strain of Marek's Disease Virus.** (Eng) Schat, K. A. (D Avian and Aquatic Animal Medicine, New York State C Veterinary Medicine, Cornell Univ., Ithaca, NY, 148 Calnek, B. W. *Infect Immun* 22(1): 225-232; 1978.

The ability of a nononcogenic strain of Marek's disease vi (SB-1) to protect against three Marek's disease-derived tun transplants was studied in intact, embryonally bursectomi (Bx), or thymectomized (Tx) or cyclophosphamide (CP)- CP/Tx-treated S, N, P, and G-Bl chickens. The chick were challenged with JMV, a non-virus-producing tra plant, or GA/Tr-1 or MDT-198, two virus-producing tra plants. Protection was significant when SB-1 (focus-forming units) and JMB (10^3 viable cells) were admi tered together, but protection was optimum when challe was performed 7 days' postvaccination. Protection was ab ished by increasing the number of JMV tumor cells to 10^5 cells or by CP/Tx treatment. Tx, CP, or Bx alone did ameliorate the immune response. Inactivated SB-1-infec cells (equivalent to 14,300 focus-forming units of live SB were unable to protect against JMV challenge. SB-1 protec against GA/Tr-1, as evidenced by enhanced tumor rejecti and the absence of metastases and virus-induced tumors, b not against MDT-198 in intact syngeneic and allogen chickens. Protection against MDT-198 was present in v cinated Bx chickens. It is concluded that protection agai JMV is T-cell-dependent and requires the induction of neo tigens not present in the inactivated SB-1 cellular prepa tion. Several possible explanations for the different respon to GA/Tr-1 and MDT-198 are given. (37 refs)

78-6407 **70 Nm Particles Detected in Lymphoblast Cell Lines Derived from Marek's Disease T mors.** (Eng) Nii, S. (Dept. Pathology, Res. Inst. Microb Diseases, Osaka Univ., Yamada-kami, Suita, Osaka, Japa Yasuda, I.; Ikuta, K. *Biken J* 20(3-4): 151-154; 1977.

The ultrastructure of the 70-nanometer (nm) particles fou in two lymphoblastoid cell lines derived from Marek's disea lymphomas (MSB-1 and MOB-1) was determined. Intran clear viral capsids of about 100 nm diameter were found a few cells from both lines, and about 25% of these ca sid-bearing cells also contained the spherical 70-nm particl

e latter were not detected in duck fibroblasts infected with rek's disease virus, although another aberrant form of the us could be found in both infected duck embryo fibroblasts l lymphoblastoid cell lines. Most 70-nm particles appeared consist of an inner spherical structure of high electron nsity and outer, radially arranged projections of moderate nsity. It is not certain whether the particles actually have ubstructure with rod-shaped projections or whether these jections represent cross-sections of strandlike structures t coil around the inner spherical structure. It is suggested t the 70 nm particle is an aberrant form of Marek's disease us. (8 refs)

-6408 **Induction of Intracranial Neoplasms by Intracerebral Inoculation of the Bratislava-77 rain of Avian Sarcoma Virus in Perinatal and Adult F344 nts: Influence of Age at Inoculation on Tumor Incidence d Morphology and Post-Inoculation Survival.** (Eng) Cope-nd, D. D. (Duke Univ., Durham, NC). *Diss Abstr Int B* (5): 2229; 1978. (no refs)

3-6409 **Modulation of Mouse Mammary Tumor Virus Production in the MJY-Alpha Cell Line.** (Eng) agi, M. J. (Dept. Neoplastic Diseases, Mount Sinai Sch. edicine, New York, NY, 10029); Blair, P. B.; Lane, M. A. *Virol* 28(2): 611-623; 1978.

roduction of mouse mammary tumor virus (MMTV) vi-ons by the mouse mammary tumor cell line MJY-alpha was own to be reversibly suppressed by in vivo implantation of e cells into isogeneic MMTV-free BALB/c or MTV-infected BALB/cfC3H mice. This suppression was pid; the decrease in MMTV particles was observed as early 7 days after implantation and it remained constant with rther in vivo passage of the MJY-alpha tumors. Examina-on of thin tumor sections by electron microscopy revealed at intracytoplasmic A particles, budding particles, and ll-free MMTV B particles were all affected. However, im-unofluorescence assays of the sections demonstrated the esence of MMTV viral antigens in the cells. Cell cultures itiated from the tumors also produced extremely low num-ers of virions during the first two passages; after this, the vel of MMTV virion synthesis increased and, in later sub-ltures, was similar to that of the parent cell line. Polypep-de profiles obtained by sodium dodecyl sulfate-polyacryla-ide gel electrophoresis of virions purified from these ltures were identical to MMTV. Immunodiffusion demon-rated a cross-reactivity between these virions and MMTV rticles obtained from mouse milk. Treatment of IJY-alpha cell cultures with rabbit anti-MMTV antiserum educed the number of extracellular MMTV virions and al-ered their electrophoretic polypeptide patterns. Possible rea-ons for virion particle suppression in vivo are given. (25 refs)

78-6410 **Mammary Tumour Virus and Casein Gene Transcription During Mouse Mammary Development.** (Eng) Pauley, R. J. (Dept. Cell Biology, Baylor Coll. Medicine, Houston, TX, 77030); Rosen, J. M.; Socher, S. H. *Nature* 275(5679): 455-457; 1978.

Mouse mammary tumor virus (MMTV) RNA and casein messenger RNA (mRNA) were quantitated in developing mammary tissue from BALB/c and BALB/cfC3H mice (strains that have a low and high incidence of mammary tumors, respectively) by molecular hybridization with specific complementary DNA (cDNA) probes to MMTV 70S RNA and casein 15S mRNA. The level of MMTV RNA in the mammary tissues was below the limit of detection in virgin and early pregnant BALB/cfC3H mice and was low (0.0014% of the RNA) in mice at midpregnancy. MMTV RNA increased to 0.0125% in the BALB/cfC3H mammary gland in late pregnancy and increased twofold after parturition. The level of MMTV RNA in BALB/c mammary tissues at all the developmental stages assayed was $\leq$ 0.0005%. Casein mRNA was present at 0.0009% of the RNA in the virgin mammary gland, at 0.0066% in early pregnancy, and at 0.365% late in pregnancy. Casein mRNA increased and was maintained at 1% of the RNA during lactation. Following weaning, casein mRNA decreased to 10% of the lactating level, but this level was higher than that observed in the virgin gland. Changes in casein mRNA levels were essentially the same in BALB/c and BALB/cfC3H mice. These studies indicate that the hormonal milieu required for mammary development and lactogenesis enhanced both casein and MMTV expression in the mammary gland of BALB/cfC3H mice. Following weaning, MMTV RNA did not decrease to the same degree as casein mRNA. Therefore, the accumulation of MMTV RNA in BALB/cfC3H mammary glands is dependent upon mammary development and influenced by differentiated mammary function. (28 refs)

78-6411 **Hormonal Induction of Mammary Tumor Viruses and Its Implications for Carcinogenesis.** (Eng) McGrath, C. M. (Dept. Biology, Michigan Cancer Foundation, 110 E. Warren, Detroit, MI, 48201); Jones, R. F. *Cancer Res* 38(11, part 2): 4112-4125; 1978.

The possibility that hormones and mouse mammary tumor virus (MuMTV) are cocarcinogenic for mammary epithelium was studied in BALB/c and BALB/cfC3H mice. Rates of premalignant (PM) and malignant (M) transformation were compared in cells carrying genetically (BALB/ç) or horizontally (BALBcfC3H) transmitted MuMTV proviral sequences in animals with or without pituitary implants to stimulate hormonal production. The carcinogenesis rate in BALB3cfC3H females was substantially faster than that in BALB3c mice, but the final mammary carcinoma incidence was about the same. Hormonal stimulation promoted PM transformations in noninfected as well as infected females, but the efficiency of PM transformation was substantially greater in infected than in noninfected females. The

rate-limiting step, which infectious MuMTV overcomes, was in PM transformation from the normal state. Integration of new MuMTV sequences in mammary cell DNA was detected by molecular hybridization in cells containing horizontally transmitted MuMTV but not in those germinally infected. MuMTV expression was changed in mammary epithelial cells during hormonal carcinogenesis. Expression of envelope glycopeptides (glycoprotein with a mol wt of 52,000; gp52) was induced, which correlates with amplification of MuMTV RNA sequence content. MuMTV RNA and gp52 were induced by dexamethasone in PM and M cells, but not in normal cells. Both PM and M cells had altered surfaces; the alteration may include membrane incorporation of MuMTV-related determinants of gp52. A hormonal cocarcinogenesis hypothesis is proposed in which expression of germinally transmitted MuMTV genes is the proximal cause of neoplastic transformation. (60 refs)

78-6412 **Occurrence of Antibody Against Intracytoplasmic A-Particles of Mouse Mammary Tumor Virus in Sera from Breast Cancer Patients.** (Eng) Ogawa, H. (Dept. Surgery, Faculty Medicine, Kyoto Univ., Shogoin-Kawahara-cho, Sakyo-ku, Kyoto 606, Japan); Tanaka, H. *Gann* 69(4): 539-544; 1978.

Antibody to intracytoplasmic A particles (pronucleocapsids of mouse mammary tumor virus) was detected in the sera of 26/43 Japanese breast cancer patients and 4/16 mammary fibroadenoma patients, but in only 4/37 controls. The antibody was detected by indirect immunofluorescence using acetone-fixed smears of A-particle-forming DBA/2 mouse leukemia cells. A-particle clusters fluoresced in discrete granules in the cytoplasm. The presence of the antibody was not correlated with a particular type of tumor histology, blood group, or clinical stage. Twenty of the breast cancer patients were followed after tumor resection: 10/13 antibody-positive patients became negative within 1 yr, and these 10 patients are apparently healthy. Three antibody-negative patients became positive after surgery, but two eventually reverted. Four patients remained negative, three of whom died or suffered a tumor recurrence. The antibody incidence in the breast cancer patients is higher than that detected previously in non-Japanese populations, and a possible ethnic difference is suggested. (28 refs)

78-6413 **Characterization of a New Virus from *Mus cervicolor* Immunologically Related to the Mouse Mammary Tumor Virus.** (Eng) Schlom, J. (Lab. Viral Carcinogenesis, Div. Cancer Cause and Prevention, NCI, NIH, Bethesda, MD, 20014); Hand, P. H.; Teramoto, Y. A.; Callahan, R.; Todaro, G.; Schidlovsky, G. *J Natl Cancer Inst* 61(6): 1509-1519; 1978.

A virus similar to the murine mammary tumor viruses (MuMTV) of the laboratory mouse *Mus musculus* was identified in the milk of *M. cervicolor popaeus* mice and charact ized. The virus was morphologically indistinguishable fr B-type MuMTV and was given the designation MC-MT Radioimmunoassays for the 52,000-dalton major envel glycoprotein and the 28,000-dalton major internal protein MuMTV demonstrated that Mc-MTV shared some antige determinants with both of these MuMTV proteins. The re tivity was different, however, from that observed with MuMTV tested from *M. musculus*. MC-MTV had a dens of 1.16 g/ml in sucrose and a virion-associated DNA polym rase with a divalent cation preference for Mg^2 over M Radioimmunoassay differentiated MC-MTV from the thr other viruses previously identified from *M cervicol* MC-MTV is the first virus from another species that is i munologically related to the MuMTV of *M. musculus*. B-ty particles similar to MC-MTV were observed in a spontaneo *M. cervicolor popaeus* mammary tumor, and they are bei characterized to determine their relationships to t milk-borne MC-MTV particles. (38 refs)

78-6414 **Detection of Mammary Tumor Virus Antigen DD/Tbr Strain Mice and the Hybrids.** (En Imai, S. (Second Dept. Pathology, Nara Medical Univ Nara, Japan). *J Nara Med Assoc* 29(2): 482-489; 1978.

Immunological methods were used to study the mode transmission of murine mammary tumor virus (MuMTV antigen expression in DD/Tbr (DD) mice. The incidence mammary tumors declined in DD mice when they wer raised by C57BL/6J mothers; the DD offspring thus raise were designated DDfB. MuMTV antigen was detected by immunodiffusion in the milk of DD mice, BfDD mic (C57BL/6J mice foster-nursed by DD/Tbr mothers), and (female BALB/c x male DD/Tbr)F_1 hybrids, but no antige was detected in DDfB, BALB/c, C57BL, or (female C57Bl x male DDf)F_1 mice. The transmission of MuMTV throug the milk in the DD strain was thus confirmed. Radioim munoassay revealed MuMTV antigen in the milk of 2/ DDfB mice and 3/6 (C57BL/6J x DDf)F_1 mice. The dat suggest that DD mice might harbor endogenous MTV. (2 refs)

78-6415 **Evidence for a Precursor-Product Relationshi Between Intracytoplasmic A Particles and Mouse Mammary Tumour Virus Cores.** (Eng) Smith, G. H (Lab. Molecular Biology, NCI, NIH, Bethesda, MD, 20014) *J Gen Virol* 41(1): 193-200; 1978.

The relationship between intracytoplasmic A particles (CAP) and mouse mammary tumor virus (MMTV) was investigated. CAP were purified from transplantable Leydig cell tumors or from primary mammary tumors in C3H/He mice. Electrophoretic and immunodiffusion techniques detected three MMTV-specific antigenic determinants in CAP (MMTV p27, p14, and p10) and provided evidence that showed that

e sizes and antigenic specificities of these determinants were nilar to those of the CAP polypeptides p82, p27, p20-18 d p15-10. The results suggest that CAP possess incom-etely processed virion proteins and are intracellular struc-ral precursors to MMTV cores. It is concluded that CAP uctural proteins are modified during maturation by pro-ase, ie, they are reduced to a size comparable to that of the ajor internal proteins of the virion and that this reaction determined by the folding of CAP proteins into the mor-ologically intact A particle. (20 refs)

3-6416 **Comparative Susceptibilities of Hybrid Mice to Four Mammary Tumor Viruses from Two ouse Strains.** (Eng) Moore, D. H. (Dept. Microbiology and mmunology, Hahnemann Medical Coll. and Hosp., Phila-lphia, PA, 19102); Merryman, C. F.; Maurer, P. H.; Holb-, J. A. *Cancer Res* 38(11, part 1): 3871-3878; 1978.

ne effect of injection of milk containing one of four different rains of murine mammary tumor virus (MuMTV) into sev-al mouse strains and their F_1 hybrids was measured by the ccurrence of mammary tumors and the presence of viral ntigen in the milk after the third and later litters. BALB/c ice were very susceptible to infection with strain A virus, ut C57BL mice and (C57BL x BALB/c)F_1 hybrids were not. rain Af virus had a low infectivity in all three groups of ice. RIII virus was very infectious in C57BL but less infec-ous in RIIIf mice. The susceptibility of (RIIIf x C57BL)F_1 ybrids was similar to that of C57BL mice. RIIIf virus was oderately infectious in RIIIf mice but poorly infectious in oth C57BL mice and (RIIIf x C57BL)F_1 hybrids. However, I was highly infectious and produced tumors at an early age n BALB/c mice and (RIIIf x BALB/c) F_1 hybrids. These esults demonstrate the marked influence that the father can xert on the susceptibility of hybrids to a particular virus. here was a good correlation between incidence of infection nd incidence of mammary tumors. These experiments point ut the complexity of the mouse assay for MuMTV and the rroneous conclusions that may be drawn from a single ex-eriment. (38 refs)

78-6417 **Suppression of Chemical (DEN) Carcinogenesis in SWR/J Mice by Goat Antibodies Against Endogenous Murine Leukemia Viruses.** (Eng) Pottathil, R. Jackson Lab., Bar Harbor, ME, 04609); Huebner, R. J.; Mei-r, H. *Proc Soc Exp Biol Med* 159(1): 65-68; 1978.

The possible involvement of endogenous murine leukemia irus (MuLV) in chemical carcinogenesis in vivo was tested sing SWR/J mice treated with diethylnitrosamine (DEN: 0 mg/kg ip). The mice were treated with goat anti-radiation eukemia virus (RadLV) and AT124 MuLV IgG before and fter DEN treatment, and their effects on the induction and atency of lung tumors were followed. Fifteen of 20 DEN-treated mice immunized with AT124 IgG died from lung tumors; 50% mortality from lung tumors occurred at 54 wk after treatment. Thirteen of 20 unimmunized controls died with multiple lung tumors; the 50% mortality occurred by the 29th wk. Mice immunized with anti-RadLV IgG survived up to 64 wk after DEN treatment, with 18/20 mice developing lung tumors; 50% mortality occurred at 58 wk. Control mice survived only to 38 wk, with 12/20 developing lung tumors. Immunized mice had larger lung tumors than nonimmunized controls. These data indicate that the survival of antiviral IgG-treated mice was signficantly prolonged over that of nonimmunized mice. The antiviral IgG's had apparently very little effect, if any, on tumor growth rate. Although the mechanism of the suppression of chemical carcinogenesis by antiviral IgG's is not clear, the findings indicate that viruses are involved in chemical carcinogenesis. (14 refs)

78-6418 **Rapid In Vitro Assay for Thymotropic, Leukemogenic Murine C-Type RNA Viruses.** (Eng) Lieberman, M. (Cancer Biology Res. Lab., Dept. Radiology, Stanford Univ. Sch. Medicine, Stanford, CA, 94305); Decleve, A.; Kaplan, H. S. *Virology* 90(2): 274-278; 1978.

The in vitro quantitation of thymotropic and leukemogenic murine C-type RNA viruses is described. When serial dilutions of murine leukemia viruses (MuLV's) from C57BL/Ka mice were plated on a nonproducer lymphoma cell line derived from a radiation-induced lymphoma of this strain, end-point titers were obtained that correlated well with those obtained by titration methods in vivo. This rapid in vitro assay may be extended to the titration of a variety of MuLV's. (14 refs)

78-6419 **Functional Macrophage Cell Lines Transformed by Abelson Leukemia Virus.** (Eng) Raschke, W. C. (Developmental Biology Lab., Salk Inst., PO Box 1809, San Diego, CA, 92112); Baird, S.; Ralph, P.; Nakoinz, I. *Cell* 15(1): 261-267; 1978.

Three cloned cell lines that express properties of macrophages were established from murine tumors induced with Abelson leukemia virus (A-MuLV). Two of the three original tumors also yielded lymphocyte cell lines, one typical of the Abelson virus disease and the other a thymic lymphoma. Two of the macrophage lines were tumorigenic when placed in syngeneic BALB/c mice, producing typical A-MuLV lymphocyte neoplasms. All three macrophage lines pinocytosed neutral red, phagocytosed zymosan and latex beads, killed antibody-coated sheep RBC targets, and secreted lysozyme. The co-isolated lymphocyte lines showed none of these properties. Of two macrophage cell lines tested, neither was capable of replacing the adherent cell population required for the induction of in vitro immune responses. Bacterial lipopolysaccharide, an agent that activates normal macrophages, specifically inhibited the growth of the transformed macrophages in culture. The secretion of A-MuLV by two of the

macrophage lines provides conclusive evidence that the Abelson virus is capable of productively infecting the macrophage cell type. The other macrophage line became positive for Abelson virus production after rescue by Moloney leukemia virus. (21 refs)

78-6420 **Translation of Type C Viral RNAs in *Xenopus laevis* Oocytes: Evidence that the 120,000-Molecular-Weight Polyprotein Expressed in Abelson Leukemia Virus-transformed Cells is Virus Coded.** (Eng) Reynolds, R. K. (Lab. Cellular and Molecular Biology, NCI, Bethesda, MD, 20014); van de Ven, W. J.; Stephenson, J. R. *J Virol* 28(2): 665-670; 1978.

The genomic RNA of two representative mammalian replication-defective transforming viruses, Abelson leukemia virus (AbLV) and woolly monkey sarcoma virus (WMSV), was purified and translated in *Xenopus laevis* oocytes. The major AbLV-specific protein synthesized was a polyprotein (pp) similar in mol wt and immunological properties to a previously described 100,000- to 130,000-dalton pp expressed in AbLV-transformed cells that contained the two amino terminal *gag* gene proteins p15 and p12. Translation of WMSV RNA resulted in the synthesis of a 55,000-dalton pp consisting of woolly helper virus p30, p15, and p12. The results establish that the nonstructural portion of the 110,000- to 130,000-dalton pp expressed in AbLV-transformed cells is virus-coded. The in vitro translation system may provide a means of testing sera from various sources for antibody directed against their nonstructural components. (20 refs)

78-6421 ***Fv*-1 Regulaton of Lymphoma Development and of Thymic, Ecotropic and Xenotropic MuLV Expression in Mice of the AKR/J x RF/J Cross.** (Eng) Mayer, A. (Dept. Genetics and Pathology, Albert Einstein Coll. Medicine, Bronx, NY, 10461); Duran-Reynals, M. L.; Lilly, F. *Cell* 15(2): 429-435; 1978.

The incidence of spontaneous thymic lymphoma in crosses between AKR/J and RF/J mice was studied. AKR mice developed almost a 100% incidence of spontaneous lymphocytic thymic lymphoma. The incidence was much lower in the (AKR x RF)F_1 hybrids and in about 50% of the (AKR x RF) x AKR backcross mice. This resistance was associated with a reduction in endogenous ecotropic and xenotropic murine leukemia virus (MuLV) expression in the prelymphomatous thymus. The data indicated that the RF mice transmitted an allele at a single locus that resulted in a dominant suppression of lymphoma-inducing, AKR-transmitted genes. This allele appeared to map at the *Fv*-1 locus closely linked to the *Gpd*-1 locus. The results indicate that the particular *Fv*-1 allele of AKR mice provides a permissive genetic background for endogenous ecotropic and xenotropic MuLV expression and that these viral activities may be etiologically involved in the development of spontaneous thymic lymphoma in the mouse. (18 refs)

78-6422 **Age-dependent Relaxation of Gene Repressi Increase of Endogenous Murine Leuke Virus-related and Globin-related RNA in Brain and Live Mice.** (Eng) Ono, T. (Gerontology Res. Center, Natl. I Aging, Baltimore City Hosps., Baltimore, MD, 21224); C ler, R. G. *Proc Natl Acad Sci USA* 75(9): 4431-4435; 19

In order to determine whether a slow loss of differentiati by epigenetic and/or mutational mechanisms could be a co mon denominator in mammalian aging, any age-depende expression of specific genes not normally expected to be pressed was investigated. ^{3}H-labeled complementary DN (cDNA) to the murine leukemia C-type RNA virus (MuL genome and globin genes were used as probes to determi the presence of RNA complementary to these genes in RN extracted from brain and liver of young (6-7 mo), m dle-aged (19-20 mo), and old (26-27 mo) C57BL/6J mi Significant amounts of globin RNA were found in brain n clei and cytoplasm. There was no age difference in the glob RNA sequences present, but the number of globin RN molecules increased from 15 in 6-mo-old mice to 34 27-mo-old animals for nuclei and from 280 to 500 for t cytoplasm. Similar results were found in the liver. RNA co plementary to the MuLV cDNA probe was also found b in contrast to globin, the different RNA sequences increas in brain and liver nuclei from about 45% of the MuL genome in 6-mo-old animals to 72% in those 27 mo old. T number of MuLV-related RNA molecules remained consta at about 22 and 38 per nuclei for brain and liver, respectivel Derepression of genes of this magnitude could result in time-dependent increase of virus-related diseases and a gene al deterioration of the organism. (34 refs)

78-6423 **Heteroduplex Analysis of the Sequence Rel tions Between the RNAs of Mink C Focus-inducing and Murine Leukemia Viruses.** (Eng) Chie Y. H. (Dept. Chemistry, California Inst. Technolog Pasadena, CA, 91125); Verma, I. M.; Shih, T. Y.; Scolnic E. M.; Davidson, N. *J Virol* 28(1): 352-360; 1978.

Electron microscope heteroduplex analysis was used to stud the sequence relationships between AKR ecotropic virus an an AKR-derived mink cell focus-inducing (MCF) isola (AKR MCF 247), between Moloney murine leukemia viru (M-MLV) and an M-MLV MCF isolate (M-MLV_{83}), and b tween AKR and M-MLV. For the MCF viral RNA of AK origin and the MCF viral RNA of M-MLV origin, th MCF-specific sequences were located in a region extendin from 1.95 to 2.75 kilobases (kb) from the 3′ end. Studies the sequence relationship between AKR and M-ML showed four major sequence nonhomology regions centere at 1.1, 2.3, 3.3, and 6.8 kb from the 3′ end of viral RNA, wit lengths of 0.5, 0.6, 0.5, and 0.5 kb, respectively. Further ob servations suggested that there is some degree of partial se quence mismatch in the entire region from 0.9 to 3.5 kb However, the AKR and M-MLV sequences immediately ad jacent to the 1.95- and 2.75-kb junctions with MCF-specifi

ences were relatively similar in AKR and M-MLV. The lts suggest that the *env* gene of MLV's maps from 1 to from the 3′ end of the genomic RNA and that the car- yl end of the glycoprotein of each MCF strain is similar dentical to that of its ecotropic parent. Thus, the physical ence from heteroduplex structures is consistent with the othesis, derived from biological properties and tryptic tide analysis, that the MCF viruses are recombinant with- he *env* gene. (25 refs)

6424 **Erythropoietin Responsiveness In Vivo of Friend Virus Target Cells for Transformation Virus Replication.** (Eng) Nasrallah, A. G. (Div. Experi- tal Biology, Baylor Coll. Medicine, Houston, TX, 30); McGarry, M. P. *Cancer Res* 38(11, part 1): 4-3778; 1978.

ivo cell transformation by Friend virus (FV) was investi- d by a technique that allows selective stimulation of the hropoietin-responsive cells (ERC) in mice with sup- ssed multipotential hemopoietic stem cells. DBA/2 mice viously made plethoric by hypertransfusion were adminis- d busulfan (BU: 60 mg/kg intragastrically) in order to press stem cell populations. On each of the following 3 s, mice received either 8 IU erythropoietin (Ep) or saline ctions. Experimental and control mice were injected with ivalent doses of polycythemia-inducing FV. A compari- of the number of target cells transformed in the mice en Ep with those not given Ep provided evidence for the C as the in vivo compartment in which the target cell for transformation resides. FV-transformed cells were deter- ned by the spleen tumor colony-forming unit assay. Differ- es in plasma virus titers in Ep-stimulated and n-Ep-stimulated mice revealed that the Ep-responsive cell predominantly responsible for the production of FV, as asured by focus-forming activity. Mice given saline and had very low levels of virus detectable in plasma ($p < 01$). Thus, the predominant in vivo target cells for FV olication and tumor colony formation reside within the ne population. (29 refs)

3-6425 **Genetic Resistance in Japanese Wild Mice (*Mus musculus molossinus*) to an NB-tropic Friend urine Leukemia Virus.** (Eng) Odaka, T. (Inst. Medical ience, Univ. Tokyo, P.O. Takanawa, Tokyo 108, Japan); eda, H.; Moriwaki, K.; Matsuzawa, A.; Mizuno, M.; Kon- , K. *J Natl Cancer Inst* 61(5): 1301-1306; 1978.

ild mice (*Mus musculus molossinus*; Sk, Hz-VI, Hz-IV, n, Mol.A, Fu, Te, and Sn) trapped in various areas of Japan re crossed with mice of inbred strains (C57BL/6, C57L, ALB/c, and C57BL/10), and their progeny were infected th NB-tropic Friend murine leukemia virus (F-MuLV: 2.5 10^5 plaque-forming units, ip) at 4 wk of age. Ten days after fection, the spleens were weighed, examined for macroscopic focal lesions, and assayed for infectious virus by the XC test. The genotypes of the wild mice were deduced from the responses of the infected progeny. Genetic analysis indicated that 4/8 mice tested had a dominant gene that suppressed virus replication; this gene resembled the *Fv-4′* allele. No mice with the *Fv-2′* allele were found. The gene resembling the *Fv-4′* allele must have an important role in the natural occurrence and propagation of MuLV in wild mice, and it may provide an explanation for the low expression of MuLV in some populations of wild mice. (22 refs)

78-6426 **Changes in Cyclic Adenosine 3′:5′-Monophosphate Levels During Induction of Differentiation in Murine Erythroleukemia Cells.** (Eng) Gazitt, Y. (Dept. Human Genetics and Development, Columbia Univ., Coll. Physicians and Surgeons, New York, NY, 10032); Reuben, R. C.; Deitch, A. D.; Marks, P. A.; Rifkind, R. A. *Cancer Res* 38(11, part 1): 3779-3783; 1978.

Evidence is presented, using synchronized (Syn) and nonsynchronized (NSyn) cultures of Friend virus-infected murine erythroleukemia cells (MELC), that several MELC differentiation-inducing agents induce both an increase in cyclic AMP (cAMP) levels and a transient prolongation of G_1. The sequential high thymidine (2 mM)-hydroxyurea (0.5 mM) method was used to synchronize the cells. Upon release from cell cycle arrest, the cells go through S in 5 hr, G_2-M in 1 hr, and G_1 in 3 hr. Syn cells exposed to the inducers hexamethylene bisacetamide, dimethyl sulfoxide, and sodium butyrate progressed through the first Syn cell cycle with the same kinetics as uninduced Syn cells, but remained in G_1 for 6-8 hr. In control cells, the cAMP level was high when cells were at the G_1-S boundary, fell during S and G_2-M, and then rose during G_1. In inducer-treated cells, there was a transient five- to sixfold increase in cAMP during mid-S. In NSyn cultures, an increase in the proportion of cells in G_1 was first noted 6-8 hr after addition of inducer and, depending on the inducer used, could still be detected 10-20 hr later. A transient two- to threefold increase in cAMP occurred 3-6 hr after addition of inducer. Two potent cyclic nucleotide phosphodiesterase inhibitors, 1-methyl-3-isobutylxanthine and RO-20-1724, also increased cAMP, prolonged G_1, and induced MELC differentiation, but two weaker inhibitors, caffeine (CF) and theophylline (TP), failed to induce differentiation. The fact that TP and CF elevated cAMP and transiently prolonged G_1 but failed to stimulate Hb synthesis suggests that these two effects may not be sufficient to trigger erythroid differentiation or that other effects of these agents prevent differentiation. The magnitude and duration of inducer-mediated prolongation of G_1 did not predict or correlate with the degree of induced differentiation. (35 refs)

78-6427 **Mechanism of Genetic Resistance to Friend Virus Leukemia in Mice. V. Relevance of *Fv-3* Gene in the Regulation of In Vivo Immunosuppression.** (Eng)

Kumar, V. (Dept. Pathology, Boston Univ. Sch. Medicine, 80 E. Concord St., Boston, MA, 02118); Resnick, P.; Eastcott, J. W.; Bennett, M. *J Natl Cancer Inst* 61(4): 1117-1123; 1978.

An attempt was made to determine if the single autosomal gene *Fv-3*, which regulates susceptibility to immunosuppression by Friend murine leukemia virus (F-MuLV) in vitro, has a similar effect in vivo. Infection of DBA/2, B10.DZ/n, and their progeny F_1 mice with F-MuLV suppressed humoral antibody synthesis in vivo and lymphocyte mitogenesis in vitro. Both these effects of F-MuLV were under host genetic control. In vitro suppression of lymphocyte mitogenesis was regulated by *Fv-3*. Genetic analyses, with the use of the susceptible DBA/2 and resistant B10.D2/n parents and their F1, intercross, and backcross progeny, indicated that a single autosomal gene dominant for susceptibility regulated the in vivo susceptibility to immunosuppression by F-MuLV. Individual [(DBA/2 x B10.D2)F_1 x B10.D2] mice were typed for susceptibility to F-MuLV-induced suppression of lymphocyte mitogenesis in vitro (an *Fv-3* function) and for susceptibility to immunosuppression by F-MuLV in vivo. This analysis indicated that the same mice that were susceptible or resistant to immunosuppression in vivo were susceptible or resistant to suppression of lymphocyte mitogenesis in vitro. Spearman's rank analysis of the data also indicated that the in vivo and in vitro immunosuppressive effects of F-MuLV were correlated with and not independent of each other. Thus *Fv-3*, which regulates the effect of F-MuLV on lymphocytes in vitro, also appears to regulate the effect of F-MuLV on antibody-forming cells in vivo. (17 refs)

78-6428 **Induction of Intracisternal A-Type Particles During Friend Cell Differentiation.** (Eng) Ostertag, W. (Max-Planck-Institut fur Experimentelle Medizin, 3400 Gottingen, W. Germany); Krieg, C. J.; Cole, T.; Pragnell, I. B.; Swetly, P.; Weimann, B. J.; Dube, S. K. *Exp Cell Res* 116(1): 31-37; 1978.

The regulation of intracisternal A-type particle synthesis during dimethylsulfoxide (Me_2SO)-induced erythroid differentiation was studied in a number of Friend cell lines under conditions which favored or restricted Friend spleen focus-forming virus (FV) production. At least three cell types were derived from the virus positive Friend cell clone F4: Class I lines (V++,A+) produced high levels of infectious FV and low numbers of A-type particles; Class II lines (V+,A++), to which Class I lines could spontaneously and reversibly shift, produced marginal FV and high numbers of A-type particles; and Class III lines (V-,A-) produced neither FV nor A-type particles. Induction of erythroid differentiation in (V+,A++) cells by Me_2SO was paralleled by an increase in C-type, but not A-type, particles. Inhibition of C-type virus production by interferon or azidoti.. midine was accompanied by a great increase in A-type particle production. A-type particle number was also increased during induction of differentiation in B8 cells, which show an endogenous defect in Friend virus synthesis (V+,A++). Neither C- nor A-type particles were induced during induction of ferentiation in Class III cells, although these cells show marginal increase in Friend C-type viral RNA levels in cytoplasm. (V+,A++) cells also showed an increas Friend virus-related RNA during differentiation. The suggest that intracisternal A-type particles in Friend cells related to Friend virus and that the increase in expressio this component is linked to, but is not conditional for, thropoietic differentiation in Friend cells. (16 refs)

78-6429 **Increase in Intracisternal A-Type Particle Friend Cells During Inhibition of Friend V (SFFV) Release by Interferon or Azidothymidine.** (E Krieg, C. J. (Max-Planck-Institut fur Experimentelle M zin, D-3400 Gottingen, W. Germany); Ostertag, Clauss, U.; Pragnell, I. B.; Swetly, P.; Roesler, Weimann, B. J. *Exp Cell Res* 116(1): 21-29; 19

The effects of interferon and azidothymidine (N_3T), wh are known inhibitors of Friend virus synthesis, on the le of intracisternal A-type particles in Friend erythroleuke (F4-6) cells were studied. Treatment with interferon (IU/ml for 4 days) or N_3T (0.25 mM for 35 hr) inhib spleen focus-forming virus (SFFV) production, reverse tr scriptase activity, and the number of C-type particles w increasing the number of intracisternal A-type particles cell 1- to 20-fold. The A-type particles released from treated cells did not differ in ultrastructure from th released from untreated cells. Interferon treatment of cells, which show an a priori low level of C-type virus synt sis, did not result in an increase in A-type particles. Simila the number of A-type particles was not increased by inter on treatment of three C-type virus-releasing cell lines, though C-type virus release was inhibited. Viral RNA le were not markedly increased during inhibition of C-t virus release in F4-6 cells. The presence and accumulat of A-type particles seems to be related to the production Friend virus complex (SFFV). (41 refs)

78-6430 **Effect of Infection of Mice with Friend L kemia Complex Viruses on Background An body-forming Cell Production In Vitro.** (Eng) Bendinelli, (Inst. Microbiology, Univ. Pisa, I-56100 Pisa, Italy); M teucci, D.; Toniolo, A.; Friedman, H. *Experientia* 34(1161-1162; 1978.

After infection of BALB/c donor mice with Friend leuke complex viruses and Rowson-Parr virus, the production vitro of background plaque-forming cells against sheep RE by spleen cells was depressed. (14 refs)

78-6431 **Specific Inhibition of XC Syncytia Formati by Anti-MuLV gp69/71 Antibodies.** (Eng) Gi

recht, S. (Laboratoire d'Immunologie et de Virologie des neurs, Inserm U-152, Hopital Cochin, 27 rue du Faurg Saint Jacques, F-75674 Paris Cedex 14, France); Blaiu, C.; Levy, J. P. *Intervirology* 10(6): 338-344; 1978.

e results of XC syncytia-inhibition tests using ecotropic rine leukemia virus (MuLV) producer cells and various iviral antisera are presented. The producer cells were: 3-FL cells infected by Gross leukemia virus (GLV); 7BL/6 mouse embryonic fibroblasts infected by Rauscher kemia virus (RLV); and (BALB/c x NIH)F_1 hybrid embnic fibroblasts infected by Moloney leukemia virus LV). Antisera used included rat antisera against LV-induced rat tumors; (W/Fu x B/N)F_1 rat anti-AT124 notropic C-type virus; mouse anti-FMR (Friend, Moloney, uscher) sera; monospecific goat antisera against RLV ypeptides p10, p12, p15, p30, p60, and gp69/71; and nor-l sera from uninoculated mice of various strains. When V producer cells were treated with RLV polypeptide anera prior to coculture with XC cells, antisera against p10, 2, p15, p30, and p60 were devoid of inhibitory activity, ereas the two anti-gp69/71 sera were strongly inhibitory, ggesting that gp69/71 mediates the fusion of mouse procer and XC cells. Since this inhibitor is specific for angp69/71, it provides a simple, sensitive, and convenient y to type ecotropic C-type viruses and to detect angp69/71 antibodies. The results with normal mouse sera ggest that older B6 mice and their F_1 hybrids with DBA/2 C3H/He spontaneously produce anti-GLV-gp69/71 anodies with type-specific activity. (17 refs)

-6432 **Sequential Changes of T- and B-Cells, Virus Antigen Expression and Primary Histologic Tuor Diagnosis in Virus-induced Lymphomagenesis of Mice.** ng) Krueger, G. R. (Immunopathologisches Laboratorin, Pathologisches Institut der Universitat Koln, Joph-Stelzmann-Strasse 9, D-5000 Cologne, W. Germany); scher, K. M.; Flesch, H. G. *Z Krebsforsch* 92(1): 41-54; 78.

and B-cell counts, estimation of immunoglobulin (Ig) ceptor fluidity, and expression of virus-coded antigens were rrelated with histological findings during the development a virus-induced mouse lymphoma. BALBc mice were inted at 4 days of age with the strongly oncogenic Moloney ukemia virus (MLV), the moderately oncogenic (in ALB/c mice) Gross passage A virus (GLV-A), or the nnoncogenic Gross 3T3 tissue culture virus (GLV-T). Rouine autopsies were done at 2- to 4-wk intervals postinjection PI). Several changes were observed in mice with MLV and LV-A infection but not in those with GLV-T infection. Ig ceptor fluidity and expression of virus antigen were deeased at the initial examination (2 wk PI). There were sigficant decreases in the percentage of T cells 9-12 wk PI, ccompanied by histologic atrophy of the thymus and of ymus-dependent regions of lymphatic tissues. The first leons histologically suspicious for lymphoma occurred in the thymus 11-12 wk PI with MLV and 12-20 wk PI with GLV-A. At 15-20 wk PI with MLV and 20-30 wk PI with GLV-A, generalized lymphoma was seen. In ultrastructural studies, there was no specific cell change indicating malignant transformation of individual cells. There was some indication of derangement and of a reduction of cytoplasmic microfilaments in proliferating lymphoblasts and lymphoma cells. (45 refs)

78-6433 **Replication-defective Ecotropic Murine Leukemia Viruses: Detection and Quantitation of Infectivity Using Helper-dependent XC Plaque Formation.** (Eng) Rein, A. (Lab. Tumor Virus Genetics, NCI, Bethesda, MD, 20014); Bassin, R. H. *J Virol* 28(2): 656-660; 1978.

An infectivity assay for a defective variant of Moloney murine leukemia virus M (MuLV-M) and for other replication-defective (R-D) ecotropic MuLV's is reported. The variant was present in a clone of mouse cells (clone 8A) isolated from a murine sarcoma virus (MSV)-transformed derivative of mouse 3T3FL cells superinfected with MuLV-M. The assay is based on the fact that some isolates of MuLV replicate well in mouse cells but, unlike nondefective ecotropic MuLV's, do not induce fusion in XC cells. Particles of R-D ecotropic MuLV, which do not themselves initiate XC plaque formation, give rise to XC plaques in cells that are coinfected with XC-negative, nondefective MuLV. Thus, fusion of XC cells is a marker by which the defective virus can be specifically detected in the presence of a nondefective virus. In two trials, clones 8A and NP-N (a non-plaque-forming variant of N-tropic MuLV) produced particles that did not form plaques in the XC test. However, these particles formed XC plaques when amphotropic MuLV, which is XC-negative, was added to the assay plates. This phenomenon can be used as a quantitative infectivity assay for R-D MuLV's. (17 refs)

78-6434 **Ornithine Decarboxylase Activity in Cells Acutely and Chronically Transformed by Murine Sarcoma Virus.** (Eng) Kilton, L. J. (NCI-VA Medical Oncology Unit, NCI, Bethesda, MD, 20014); Gazdar, A. F. *Proc Soc Exp Biol Med* 159(1): 142-147; 1978.

Three contact-inhibited or murine sarcoma virus (MSV)-transformed clones of BALB/3T3 mouse cells were transformed or supertransformed by MSV or its accompanying nontransforming helper virus (murine leukemia virus, MuLV), and the relationships between ornithine decarboxylase ODC activity, morphology, virus production, and growth rates were examined. Clones isolated from these lines were also studied. All of the virus-infected lines released both MSV and MuLV. ODC activities could not be correlated with difference in growth rates or with release of transforming or nontransforming viruses. The only consistent relationship was between elevated ODC activity and acute morphological transformation. With cell passage, ODC levels of acutely

transformed cells returned to baseline levels, perhaps because most acutely transformed cells fail to divide. These findings plus those of a previous study, which indicated that human cytomegalovirus infection of fibroblasts overrides end product repression of ODC by putrescine, suggest that the oncogenic potential of a virus may be related to its ability to interfere with normal regulatory functions of key cellular metabolic enzymes. (16 refs)

78-6435 **Enhanced Susceptibility of Virus-Infected Cells to Starch-induced Peritoneal Exudate Cells.** (Eng) Goldman, R. (Dept. Zoology, Univ. Coll. London, Gower St., London, WC1E 6BT, England); Hogg, N. *In: The Macrophage and Cancer. Proceedings of the European Reticuloendothelial Society Symposium held in Edinburgh, September 12-14, 1977.* European Reticuloendothelial Society (Edinburgh, Scotland): 448 pp.; 97-107; 1977.

Starch-induced peritoneal exudate cells from BALB/c mice were tested for their ability to inhibit 5-^{125}-I-iodo-2′-deoxyuridine (IUDR) incorporation in normal, virus-infected, or virus-transformed mouse embryo fibroblasts (MEF). Preliminary experiments showed that the PEC abrogated IUDR incorporation in K-BALB cells, and that this cytostatic activity resided in the adherent cell fraction of the PEC, which included macrophages but not T or B lymphocytes. Recently explanted MEF were relatively resistant to PEC-mediated cytostasis. However, secondary MEF transformed by murine sarcoma virus or infected with murine leukemia virus, Sendai virus, or influenza virus were sensitive to PEC cytostasis. Virus-infected or -transformed MEF from four mouse strains (BALB/c, CBA, AKR, C57BL) were affected to a similar degree, indicating that there is no requirement of H-2 compatibility between effector and target cells. These results show that membrane alterations induced by a nontransforming virus infection are sufficient to render cells susceptible to activated, adherent PEC. (26 refs)

78-6436 **Structural Markers on Core Protein p30 of Murine Leukemia Virus: Functional Correlation with *Fv-1* Tropism.** (Eng) Gautsch, J. W. (Res. Inst. Scripps Clinic, 10666 N. Torrey Pines Road, La Jolla, CA, 92037); Elder, J. H.; Schindler, J.; Jensen, F. C.; Lerner, R. A. *Proc Natl Acad Sci USA* 75(9): 4170-4174; 1978.

The primary structure of the major core protein, p30, of murine leukemia virus (MuLV) was studied in over 50 virus isolates by a simplified method of in situ radioiodination and two-dimensional peptide mapping. Although all MuLV p30's displayed a close structural similarity, minor differences in the peptide profiles did occur, and they were reproducible and served as excellent markers for certain MuLV strains. A loss of peptide spots 1 and/or 2 in the peptide map was noted only in Friend, Moloney, and Rauscher leukemia viruses, and not endogenous MuLV. Peptide 12, which varied in its relative position more than any other peptide in the maps, exhibited one of four primary positions, and was to be functionally associated with *Fv-1* tropism. On this b a virus could be classified as N-tropic, B-tropic, xenotro and/or from a wild mouse. Although phenotypically ide cal, two BALB/c B-tropic isolates, WN1802B and B could be genotypically distinguished, as could two diffe BALB/c xenotropic viruses, B-228 and Mk-137MC. The clone of Moloney murine sarcoma virus was seen to pos extra marker peptides derived from the COOH end of that could be sarcoma-associated. (38 refs)

78-6437 **Further Evidence for Deletion of Envel Glycoprotein (gp69/71) Sequences in Forma of Moloney-Murine Sarcoma Virus.** (Eng) Peebles, P. (Lab. Tumor Virus Genetics, NCI, Bethesda, MD); Stra M.; August, J. T. *J Gen Virol* 40(3): 503-510; 1978.

The S+L-strain of Moloney murine sarcoma virus (M-MS was nonproductively cloned in S+L-mouse, dog, mink, human cells, and expression of the Moloney murine leuke virus (M-MuLV) 30,000-mol wt core protein (p30) and velope glycoprotein (gp69/71) was studied by radio munoassay. In all cases, the p30 determinant, which has b demonstrated to be part of a larger p60 protein precurs remained associated with the MSV genome. However, heterologous host S+L- cell line showed evidence for M-MuLV gp69/71. These data support previous biologi data and suggest that the gp69/71 gene was deleted in formation of this MSV genome. The S+L- dog cells releas large amounts of a soluble p30 antigenic determinant i their culture supernatant fluids in the absence of detecta virus particle production and under optimal conditions cell viability. This is the first example of the in vitro rele of a major structural core virus protein in soluble form in absence of virus particle production. (31 refs)

78-6438 **Biochemical Studies on RNA Tumor Virus formation and its Transmission in B16 Muri Melanoma.** (Eng) Hehlmann, R. (Med. Poliklinik, Univ sitat Munchen, Munich,W.Germany); Erfle, V. *Int J Can* 22(5): 630-638; 1978.

The RNA tumor virus information of the B16 mouse melan ma system and its transmission were studied biochemicall Density-fractionated B16 melanomas contained particl possessing a 70S RNA associated with a reverse transcri tase. The particles had a density of 1.14-1.18 g/cm^3 along 25%-55% sucrose gradient. The ^{3}H-complementary DN synthesized by these particles hybridized back to its templa RNA. The B16 particle RNA showed considerable homolog with the RNA's of the murine leukemia-sarcoma virus AKR-MuLV, Kirsten-MuSV, and Rauscher-MuLV a some degree of homology to the RNA's from simian sarcom virus and RD-114 viruses. In addition, the B16 DNA co

ned particle-related sequences not present in the DNA of rmal C57BL mice. (30 refs)

-6439 **Chemical Determination of the m1 Moloney Sarcoma Virus pP60*gag* Gene Order: Evidence Unique Peptides in the Carboxy Terminus of the Polyotein.** (Eng) Oskarsson, M. K. (Lab. DNA Tumor Viruses, CI, Bethesda, MD, 20014); Elder, J. H.; Gautsch, J. W.; rner, R. A.; Vande Woude, G. F. *Proc Natl Acad Sci USA* (10): 4694-4698; 1978.

e gene order of the m1 isolate of Moloney sarcoma virus 1MSV) specific polyprotein pP60*gag* (P60) was determined by direct chemical analysis. P60 was cleaved with anogen bromide (CNBr) into eight partial and complete gments ranging from 10,000 daltons to 58,000 daltons. ptide maps of these fragments were compared with maps p15, p12, and three CNBr fragments of p30. The polarity p15 and p12 in a CNBr fragment of P60 was determined carboxypeptidase A digestion; the CNBr fragments of p30 re ordered by aminopeptidase digestion. The linear arngement of P60 CNBr fragments gave the gene order of H_2-p15-p12-p30-COOH. This linear arrangement of CNBr gments should facilitate primary amino acid sequence alysis of the polyprotein. In addition, as demonstrated with 3MSV P70, this map should serve as a useful basis for comrison to other MSV or Moloney murine leukemia virus LV) *gag* polyproteins when the latter are available in suffint quantities. The m3 isolate of MSV expressed a P70 *gag* lyprotein. Peptide maps of 48,000-dalton CNBr fragments m3 P70 and ml P60 were similar, which suggested that th polyproteins were similar through the NH_2-terminal o-thirds of p30. However, the presence of peptides unique the 10,500-dalton COOH-terminal fragment of mlMSV 0, ie, peptides absent in the p30 of either m3MSV or MLV, ggested that the *gag* gene deletion in the ml isolate begins the p30 reading frame. (21 refs)

-6440 **Feline Sarcoma Virus In Vitro Infection of Human Cells. Influence of Chemical Carcinogens Focus Formation.** (Eng) Blakeslee, J. R. (Dept. Veterinary thobiology, Coll. Veterinary Medicine, Ohio State Univ., 25 Coffey Road, Columbus, OH, 43210); Milo, G. E. *Chem ol Interact* 23(1): 1-11; 1978.

e effects of benzo(a)pyrene (BP), aflatoxin B_1 (AFB), and acetoxy-2-fluorenylacetemide (A-AAF) on Synder-Theilfeline sarcoma virus-induced focus formation was studied ng normal human foreskin fibroblasts (D550). Focus foration was inhibited by 27% to 60% in cells treated with (1.0-15.0 μg/ml) 24 hr before virus infection, by 65% to % in cells treated 6 hr before infection, by 59% to 87% cells treated 2 hr before infection, and by 31% to 42% in ls treated after infection. A 43% inhibition occurred in ls treated with A-AAF (1.0 μg/ml) 6 hr before infection, 70% in cells treated 2 hr after infection, and 55% in cells treated 24 hr after virus adsorption. AFB inhibited focus formation by 39% in cells treated with 1.0 μg/ml 6 hr before virus infection and by 46% to 59% in cells treated with 0.1 μg/ml after infection. Focus formation was not significantly altered by treatment before or after infection with pyrene (10 μg/ml) or 0.1 μg/ml A-AAF or by treatment before infection with 0.1 μg/ml AFB. Focus formation was not inhibited in cells treated with BP (15 μg/ml) or AFB (0.1 μg/ml) 48 to 96 hr postinfection. Virus-directed RNA-dependent DNA polymerase activity was not reduced in cells showing significant inhibition of focus formation, and no infectious virus was detected in either treated or untreated virus-infected cells. The data indicate that the inhibitory effect on focus formation is chemically mediated, whereas the inhibition of virus synthesis is not. (14 refs)

78-6441 **Endogenous Feline Oncoviruses: Genome Expression of RD-114 and Feline Leukemia Virus in Normal and Abnormal Differentiation of the Domestic Cat (*Felis catus*).** (Eng) Niman, H. L. (Univ. Southern California, Los Angeles, CA, 90007). *Diss Abstr Int B* 39(5): 2131; 1978. (no refs)

78-6442 **Feline Leukemia Virus Envelope Glycoprotein Vaccine: Preparation and Evaluation of Immunizing Potency in Guinea Pig and Cat.** (Eng) Salerno, R. A. (Div. Virus and Cell Biology Res., Merck Inst. Therapeutic Res., West Point, PA, 19486); Lehman, E. D.; Larson, V. M.; Hilleman, M. R. *J Natl Cancer Inst* 61(6): 1487-1493; 1978.

Envelope glycoprotein (gp) of feline leukemia virus (FeLV), strain FeLV-1, was extracted with 2% Triton X-100 and 0.43 M sodium chloride in 10 mM Tris (pH 7.5) and purified by ion-exchange chromatography on phosphocellulose. Purified FeLV envelope gp75 (mol wt 75,000 daltons) induced antibodies of high titer in goats. These antibodies specifically neutralized FeLV, precipitated radiolabeled FeLV envelope gp75, and lysed FL74 cells. Administration of 20 μg gp75 to guinea pigs in alum or adjuvant 65 induced neutralizing antibody [geometric mean titer (GMT), 8-25], radioimmune precipitating antibody (GMT, 1,382-6,450), and cytotoxic antibody (titer, ≥ 2) in all animals. Aqueous gp75 vaccine induced neutralizing antibody (GMT, <4) in only 50% of the guinea pigs. Specific-pathogen-free cats immunized with 40 μg gp75 in alum or Freund's adjuvant developed radioimmune antibody with GMT's of 127-207 (100% seroconversion, SC), but little or no neutralizing antibody (22%-38% SC; GMT, <2) or cytotoxic antibody (0%-44% SC) developed. These findings indicate that oncovirus subunit vaccines will require highly effective immunologic adjuvants to enhance the immunogenicity of the antigen in the homologous host. (36 refs)

78-6443 **Feline Oncornavirus-associated Cell Membrane Antigen.** (Eng) Essex, M. (Dept. Microbiology, Harvard Univ. Sch. Public Health, Boston, MA, 02115); de Noronha, F.; Oroszlan, S.; Hardy, W. D. *In: Prevention and Detection of Cancer. Proceedings of the Third International Symposium on Detection and Prevention of Cancer Held by the International Study Group for the Detection and Prevention of Cancer in New York, April 26 - May 1, 1976.* International Study Group for the Detection and Prevention of Cancer. (New York, NY): Vol. 2(part 1), 2404 pp.; 1401-1414; 1978.

The object of this study was twofold: (1) to determine if feline leukemia virus (FeLV) proteins gp70, p27, and p15 were detectable on the surface of feline leukemia or lymphoma cells (including cell culture lines and freshly biopsied tumor cells) and (2) to determine if feline oncornavirus-associated membrane antigen (FOCMA) activity (found naturally in healthy virus-exposed cats) could be adsorbed or removed with either pure intact or fractionated FeLV. Monospecific goat or rabbit antisera to gp70, p27, and p15 indicated that these antigens are present on FOCMA-positive cells that produce FeLV, including two cultured lymphoblastoid lines and biopsied cells from cats with naturally occurring leukemia and lymphoma. However, the antibody activity from these monospecific antisera was readily removed by adsorption with either pure gp70, p27, or p15 or whole disrupted FeLV. In contrast, similar treatment of feline sera containing high titers of FOCMA antibody did not remove antibody activity directed to the surface of virus-producer tumor cells. It is concluded that FOCMA contain antigenic determinants that are not shared with the major virus structural proteins. (43 refs)

78-6444 **Characterization of a Feline Sarcoma Virus-coded Antigen (FOCMA-S) by Radioimmunoassay.** (Eng) Sherr, C. J. (Lab. Viral Carcinogenesis, NCI, NIH, Bethesda, MD, 20014); Todaro, G. J.; Sliski, A.; Essex, M. *Proc Natl Acad Sci USA* 75(9): 4489-4493; 1978.

The previously detected expression of a feline oncornavirus-associated cell membrane antigen (FOCMA) on feline sarcoma virus (FeSV)-transformed rat and mink nonproducer cells (FOCMA-S) provided evidence that this antigen is encoded by a feline C-type viral gene. The presence of FOCMA-S in FeSV pseudotype particles facilitated the development of a radioimmunoassay (RIA) for an FeSV gene product that uses rabbit antiserum and protein derived from viral particles produced by nonfeline (mink, rat) cell. Thus, it was possible to assay for FOCMA-S with reagents generated completely outside of the feline system. Although the polyprotein (p85) detected in pseudotype virions contained p15 and p12 antigenic determinants, antibodies to these could be adsorbed with purified feline leukemia virus (FeLV) proteins. Hence, the RIA for FOCMA-S did not detect the major viral structural protein antigens found in p85. The adsorbed rabbit antiserum bound to antigenic determinants also present in p85 and reacted specifically in immunofluorescence tests rat cells transformed by FeSV and with FOCMA-positiv lymphoid tumor cells. Competition assays detected F MA-S in pseudotype C-type viruses rescued FeSV-transformed mink and rat cells, but not in heterolo C-type helper viruses or in FeLV. A cross-reactive ant was also detected in pseudotype of Kirsten sarcoma v This quantitative assay could also be used to purify sin antigens from transformed cells and to characterize these tential 'transforming proteins.' (26 refs)

78-6445 **Demonstration of Two Distinct Classes of vine Papilloma Virus.** (Eng) Lancaster, W (Div. Otolaryngology, Case Western Reserve Univ., Cl land, OH, 44106); Olson, C. *Virology* 89(2): 372-379; 1

The purpose of this study was to determine if different cla of bovine papilloma virus (BPV) exist. Virus DNA was iso ed and purified from 10 naturally occurring cases of bo fibropapillomatosis and hybridized to labeled BPV D Results indicate that two distinct classes of BPV can be tinguished based on the extent of hybridization. Satura hybridization showed that the two virus classes sha 52%-58% of their polynucleotide sequences. DNA-D reassociating kinetics revealed that the two virus classes common base pairs along 45% of the genome. The vir differed in their ability to hemagglutinate mouse RBC, they were antigenically cross-reactive but not identical complement fixation and hemagglutination inhibition. though many of the structural proteins of the two v classes seemed to have similar electrophoretic mobilitie sodium dodecyl sulfate-polyacrylamide gels, a more deta analysis will be required to detect minor differences in wt. There were no differences between the viruses with spect to location or morphology of papillomas or to a pr lection for a given bovine breed. (23 refs)

78-6446 **Common Membrane Neoantigens on Bov Papilloma Virus-induced Fibroma Cells fr Cattle and Horses.** (Eng) Barthold, S. W. (Section Compa tive Medicine, Yale Univ. Sch. Medicine, New Haven, 06510); Olson, C. *Am J Vet Res* 39(10): 1643-1645; 197

Bovine papilloma virus (BPV)-induced fibroblastic tumor cattle, horses, and hamsters were studied by indirect munofluorescence in order to identify common antigens. S en calves <2 wk old and six adult ponies were inocula id with 0.1-0.2 ml of 20%-30% BPV homogenate in multi sites. Serum was collected at inoculation and at various sp fied times afterward. Nine outbred Syrian hamsters w inoculated sc with 0.2 ml of homogenate, and a tumor fr one of these hamsters was transplanted sc into 13 oth Four calves developed fibromas, three fibropapillomas. ponies developed fibromas. Seven of nine hamsters develo fibrosarcomas, and all those with transplanted tumor de

ed large sarcomas. Specific membrane IF occurred on bo-
e and equine tumor explant cells, but not on normal der-
l cells, if reacted against homologous or heterologous sera.
cept for two bovine sera, the reactions of bovine sera to
ine tumor cells and equine tumor cells were similar. The
ction pattern of equine sera was similar, but seemed to be
dified by tumor size of the serum source. The reaction
ld be blocked in both species by homologous, but not
erologous, sera. Sera from tumor-bearing hamsters had no
ectable reactivity to cell membranes of hamster, bovine,
equine cells. Internal neoantigens were not found in any
the acetone-fixed tumor cells, using sera from the three
cies. Both tumor and normal cells were found free of BPV
igen by direct IF. (30 refs)

6447 **Replication of Nondefective Parvoviruses: Lack of a Virion-associated DNA Polymerase.** (Eng) tchard, C. (Dept. Biology, Virginia Polytechnic Inst., icksburg, VA, 24061); Patton, J. T.; Bates, R. C.; Stout, R. *J Virol* 28(1): 20-27; 1978.

ur nondefective parvoviruses, bovine parvovirus (BPV), l, LuIII, and Kilham rat virus (KRV), were examined for ion-associated DNA polymerase activity. Virions were rified from neuraminidase-treated infected cell lysates by pycnic centrifugation in CsCl or from infected cell materi-y by $CaCl_2$ precipitation and centrifugation through sucrose o CsCl. BPV and KRV preparations obtained by the for-r procedure contained DNA polymerase activity but were free of contaminating cellular proteins. In both cases, the atest amount of residual enzyme activity consisted of NA polymerase β. The latter method produced viral prepa-ions free of contaminating cellular proteins, and no DNA ymerase activity was detected in any of the four viruses. sruption of infectious virions obtained by the second meth-with ionic and nonionic detergents and sonic treatment l not result in the detection of a DNA polymerase. The ological activity and purity of each of the viruses were de-mined by hemagglutination and infectivity assays, polya-ylamide gel electrophoresis, and electron microscopy. In ch case, the virions banding at a density of 1.39-1.41 g/cm^3 CsCl were infectious and contained only the virion struc-al proteins. DNA polymerase activity was not detected in y of the purified virus preparations. It is concluded that RV, BPV, H-1, and LuIII do not contain an essential vi-n-associated DNA polymerase required for productive in-tion. (25 refs)

-6448 **Viral DNA Synthesis in Cells Infected with Temperature-sensitive Mutants of Herpes Simplex Virus Type 1.** (Eng) Bone, D. R. (Tumor Virology Lab., lk Inst. Biological Studies, San Diego, CA, 92112); Brown, .; Crombie, I.; Francke, B. *J Virol* 28(1): 14-19; 1978.

mperature-sensitive (*ts*) mutants of herpes simplex virus type 1 (HSV-1) representing eight DNA-negative (DNA-) complementation groups were characterized in temperature-shift experiments. Viral DNA synthesis was measured in mutant-infected baby hamster kidney (BHK-21) cells after (a) shift-up to the nonpermissive temperature (39 C) to determine whether synthesis continued or was inhibited and (b) shift-down to the permissive temperature (32 C) in the presence and absence of inhibitors of protein and RNA synthesis. The mutants could be grouped into three categories based on the results of these experiments. (1) After shift-up, viral DNA synthesis was inhibited in cells infected with *ts*B, *ts*H, and *ts* J, indicating that the B, H, and J proteins are continuously required for this process. Cells infected with *ts*B and *ts*H synthesized viral DNA after shift-down in the absence of de novo RNA and protein synthesis; *ts*J-infected cells did not synthesize viral DNA in the absence of protein synthesis. (2) Viral DNA synthesis continued after shift-up in cells infected with *ts*D and *ts*K but not after shift-down in the absence of RNA and protein synthesis, suggesting that these mutants are defective in early regulatory functions. (3) Cells infected with *ts*L, *ts*S, and *ts*U synthesized viral DNA after shift-up and after shift-down in the absence of RNA and protein synthesis. The functions of the L, S, and U proteins were not clarified. (11 refs)

78-6449 **Frequency of Anti-AG-4 Antibody in Patients with Uterine Cervical Cancer and Controls.** (Eng) Kawana, T. (Dept. Obstetrics and Gynecology, Faculty Medicine, Univ. Tokyo, Hongo 7-3-1, Bunkyo-ku, Tokyo 113, Japan); Sakamoto, S.; Kasamatsu, T.; Aurelian, L. *Gann* 69(4): 589-591; 1978.

The association of herpesvirus type 2 (HSV-2) with cervical cancer was investigated by determining the prevalence of antibody to an early antigen (Ag-4, an antigen that is induced in Hep-2 cells by HSV-2 4 hr after infection) in 33 Japanese cancer patients and 30 age-matched controls. A microquantitative complement fixation assay detected antibody Ag-4 in 17/33 patients and 5/30 controls. There was a tendency for antibody prevalence to increase with clinical stage: 43% at Stage I, 63% at Stage II, and 75% at Stage III. A neutralization kinetics assay showed that 11/15 anti-Ag-4-positive sera contained neutralizing antibody to HSV-2, as did 11/16 anti-Ag-4-negative sera. Eleven of 22 HSV-2-positive sera were also Ag-4-positive, which indicates that there is no correlation between the prevalance of Ag-4 antibody and that of HSV-2 neutralizing antibody. Thus, Ag-4 differs from viral antigens involved in neutralization. These results, similar to those of several US studies, suggest that HSV-2 is associated with cervical cancer and appears to reflect tumor progression. There are two possible explanations for the observation that only 17/34 patients were Ag-4-positive: antibody levels in the negative patients were too low for detection or the negative patients were not previously exposed to HSV-2. The latter explanation suggests that HSV-1 may be associated with cervical cancer in Ag-4-negative patients. (10 refs)

78-6450 **Selective Stimulation and Differentiation of Early Antigens in Lymphoblastoid Cell Lines Producing Epstein-Barr-Like Viruses.** (Eng) Neubauer, R. H. (Viral Oncology Program, Frederick Cancer Res. Center, Frederick, MD, 21501); Rabin, H.; Brown, A. M. *J Gen Virol* 41(2): 295-301; 1978.

The early antigens (EA) of Epstein-Barr virus (EBV), *herpesvirus papio, herpesvirus pongo,* and *herpesvirus pan* were examined using a procedure that combines antigen stimulation with inhibition of late virus functions and results in the selective stimulation of EA. Treatments combining 5-iodo-2′-deoxyuridine and phosphonoacetic acid (PAA) resulted in the selective stimulation of EA in lymphoblastoid cell lines that produce EBV-related viruses. The marked increase in the frequency of EA-positive cells in the relative absence of virus capsid antigens permitted the comparison of EA in related viruses. The EA's of the four viruses were distinguishable, with the greatest differences being between EBV and *h. papio.* The differences were indicated by the ability to select sera that had positive reactivity only with the homologous antigen and by differences in homologous and heterologous titers in certain cross-reacting sera. These differences were also demonstrable for both the restricted and diffuse components of EA, and, they suggest that EBV-related viruses can be distinguished by their early antigens as well as by comparisons of virus-specific nuclear antigens and DNA hybridization techniques. (11 refs)

78-6451 **Chloroquine Enhances Epstein-Barr Virus Expression.** (Eng) Karmali, R. A. (Dept. Pathology, Sch. Medicine, East Carolina Univ., Greenville, NC, 27884); Horrobin, D. F.; Menezes, J.; Patel, P.; Musto, J. *Nature* 275(5679): 444-445; 1978.

The effect of chloroquine (CQ), an antimalarial agent, on the expression of Epstein-Barr virus (EBV) antigens was studied in the Raji cell line, which is EBV-induced nuclear antigen (EBNA)-positive, early antigen (EA)-negative, and virus capsid antigen (VCA)-negative. The cells were superinfected with the P3HR-1 strain of EBV for the induction of EA and VCA. CQ was added to the infected cells, and the cultures were incubated for 48 hr. Indirect immunofluorescence showed that 6.5% of the infected cells were EA-positive. Following treatment with 0.1, 1.0, or 5.0 μg/ml CQ, however, 19%, 16.8%, and 18.3% of the cells were EA-positive, respectively. (Plasma concentrations of CQ in humans during malaria chemotherapy are 0.16-0.53 μg/ml.) There was no difference in VCA-positive cells in the presence of CQ. These results suggest that CQ may be acting either directly on the exogenous EBV genome or indirectly, by activating cellular mechanisms essential for its expression. Therefore, CQ may play an important part in the development of African Burkitt's lymphoma by enhancing EBV expression. (26 refs)

78-6452 **Longitudinal Study of Epstein-Barr Virus Antibody Titers and Excretion in Pediatric Patients with Hodgkin's Disease.** (Eng) Lange, B. (Div. Onco Children's Hosp. Philadelphia, Philadelphia, PA, 19104) beter, A.; Hewetson, J.; Henle, W. *Int J Cancer* 2 521-527; 1978.

An attempt was made to provide evidence of the latent acter of Epstein-Barr virus (EBV) infection by monitori children with Hodgkin's disease (HD) and a history of infection for changes in the titers and spectra of antib to EBV-determined antigens, excretion of the virus int oropharynx, EVB-carrying lymphoid cells in the perip blood, and clinical parameters signifying a reactivation latent viral condition. Although the incidence and geom mean titers of IgG antibodies to viral capsid antigen (V in the HD patients were similar at diagnosis to those of trols, the anti-VCA titers rose significantly above contro els during and after therapy and remained elevated thro out the 7 yr of observation. At no time were heteroph VCA-specific IgM antibodies detected. Antibodie EBV-induced early antigens were much more common (vs 9%) and antibody levels to EBV-associated nuclear gen were significantly lower in HD patients than in con No specific clinical alterations were correlated with the vated antibody titers or the observed increase in EBV e tion. Although a reactivation of EBV infection by the munosuppressive effects of HD or its therapy is presentl best explanation of these results, direct evidence has y be provided. (38 refs)

78-6453 **Isolation of a Herpesvirus-specific I Polymerase from Tissues of an American tient with Burkitt Lymphoma.** (Eng) Allaudeen, H. S. (I Pharmacology, Yale Univ. Sch. Medicine, New Haven, 06510); Bertino, J. R. *Proc Natl Acad Sci USA* 7 4504-4508; 1978.

A DNA polymerase (Pase) isolated from a 27-yr-old w American man with Burkitt's lymphoma (BL) showed s properties of herpes simplex virus (HSV)-induced DNA and the Epstein-Barr virus (EBV) DNA Pase of Burkitt in culture. The enzyme was partially purified from a mass and separated from the cellular DNA Pases. The DNA Pase, which represented 27%-30% of the total cell DNA activity, differed from the cellular DNA Pases. Its wt was determined to be 90,000 by velocity sedimenta The activity of the enzyme increased three to four time the presence of high salt concentrations (100 mM), sim to HPV DNA Pase. This enzyme further resembled I DNA Pase in its primer template preference, high mon lent cation requirement for activity, and sensitivity to p phonoacetate inhibition. N-Ethylmaleimide had no effec its activity. HSV DNA Pase antiserum inhibited the acti of BL DNA Pase, whereas antibody to HeLa cell DNA I α or to DNA Pase γ from human lymphoblast cells did Although the patient's serum contained a high EBV t addition of the serum to the assay mixture did not have effect on the activity of BL DNA Pase. Spleen and liver

s did not contain HSV DNA Pase. Detection of the HSV
A Pase in BL tissue provides additional evidence for the
ociation of EBV with this malignancy. (17 refs)

6454 **Induction of Nuclear Antigen (EBNA) Synthesis Without Transformation in Human Cord mphocytes by P3HR-1 Strain of Epstein-Barr Virus.** ng) Yamamoto, N. (Dept. Microbiology, Kumamoto iv. Medical Sch., Kumamoto, 860, Japan); Hinuma, Y. *ology* 89(2): 623-626; 1978.

e transforming potential of the P3HR-1 strain of Epin-Barr virus (EBV) was analyzed by clonal transformain soft agar, and EBV-determined nuclear antigen (EBA) induction by this virus was investigated in primary tures of normal umbilical cord lymphocytes. The B95-8 ain of EBV was used as a positive control. Experiments h six cord cell preparations from different neonates owed that all nine preparations of P3HR-1 virus gave nega- transformation results, but all cell preparations infected h B95-8 virus were transformed. In addition, EBNA-posie cells were present in all P3HR-1-infected cultures. NA synthesis without transformation was confirmed ough colcemid treatment of P3HR-1-infected cord cells. labeled cells were found upon autoradiographic examinan of cells infected with P3HR-1 and exposed to ^{3}H-thymie at several intervals after infection. It is concluded that NA synthesis does not correlate with transformation and at DNA synthesis is not necessary for EBNA induction. refs)

-6455 **Epstein-Barr Virus and Human Chromosomes: Close Association of the Resident Viral Genome d the Expression of the Virus-determined Nuclear Antigen BNA) with the Presence of Chromosome 14 in Huan-Mouse Hybrid Cells.** (Eng) Yamamoto, K. (Dept. rology, Cancer Inst., Hokkaido Univ. Sch. Medicine, 060 pporo, Japan); Mizuno, F.; Matsuo, T.; Tanaka, A.; onoyama, M.; Osato, T. *Proc Natl Acad Sci USA* 75(10): 55-5159; 1978.

ourteen hybrid clones derived from fused cultures of human mphoblastoid FV5 cells and 5-bromodeoxyuridine-resistt mouse fibroblastic MCB2 cells grown in hypoxanine/aminopterin/thymidine selective medium were exmed for the presence of Epstein-Barr virus (EBV) DNA, pression of the virus-determined nuclear antigen (EBNA), nd the presence of human chromosomes. When tested 3 mo ter their isolation, 11 of the hybrid clones were positive for BNA, but when tested 18 mo after their isolation, only 3 ones were positive for EBNA. EBV DNA was detected only the three clones that were positive for EBNA after 18 mo. hromosome analysis of the hybrid clones showed that huan chromosome 14 was common to all three positive clones, hereas this chromosome was not present in any of the negative clones tested. In 10 subclones isolated from one of the positive clones, a concordant segregation of EBNA, EBV DNA, and chromosome 14 was evident. The data suggest that the resident EBV genome is closely associated with chromosome 14 and that the presence of this chromosome alone is sufficient for the maintenance and expression of EBV genetic information in human lymphoblastoid cells. (20 refs)

78-6456 **Studies of Epstein-Barr Virus (EBV)-Associated Nuclear Antigen: Solubilization from Raji Cell Chromatin with 5 M-Urea-2 M-NaCl and Fractionation on Hydroxyapatite.** (Eng) Brown, T. D. (Beatson Inst. Cancer Res., Wolfson Lab. Molecular Pathology, Bearsden, Glasgow G61 IBD, Scotland); Rickwood, D.; MacGillivray, A. J.; Klein, G. *J Gen Virol* 40(3): 511-517; 1978.

A ^{125}I-IgG absorption assay was used to detect Epstein-Barr virus-associated nuclear antigen (EBNA) solubilized from Raji cell chromatin by treatment of the chromatin with high concentrations of urea and salt. The chromatin was fractionated into histone and nonhistone fractions on hydroxyapatite (HAP), and the nonhistone proteins were subfractionated by a discontinuous elution system. Very little antigenic activity was present in the histone-containing HAP 1 fraction, but activity was readily detected in the three nonhistone fractions (HAP 2, 3, and 4). The absorption patterns of HAP 3 and HAP 4 differed, suggesting a fractionation of antigenic specificities. HAP 3 and 4 contained the bulk of the antigenic activity but only 7% of the total chromatin protein. The data suggest that EBNA is a nonhistone chromatin-associated protein. (27 refs)

78-6457 **Alkaline Phosphatase in Epstein-Barr Viral Nuclear Antigen-positive Cell Lines.** (Eng) Karpas, A. (Dept. Haematological Medicine, Univ. Cambridge, Cambridge, England); Hayhoe, F. G.; Greenberger, J.; Neumann, H. *Science* 202(4365): 318-319; 1978.

Alkaline phosphatase (APase) present in Epstein-Barr viral nuclear antigen (EBNA)-positive, surface membrane immunoglobulin (SmIg)-negative cell lines established from two leukemia patients was characterized. One of the patients had acute myeloid leukemia (AML) and the other a combined B- and T-cell acute lymphoblastic leukemia (ALL). The AML-derived cells contained myeloid APase, as determined by its ability to catalyze the hydrolysis of two types of substrates, ortho-substituted monoesters of orthophosphoric acid (substrate type 1) and the S-substituted monoesters of thiophosphoric acid (substrate type 2) with equal efficiency. The ALL-derived cells contained lymphoid APase, which catalyzes the hydrolysis of substrate type 1 only. Biochemical testing for two types of APase may allow distinction between primitive lymphoid and myeloid cells and may also be useful for detecting APase in cells that are cytochemically negative for the enzyme. The presence of the myeloid-specific enzyme

in an SmIg-negative cell line suggests that the line is composed of myeloid precursor cells and that such cells may be susceptible to infection with Epstein-Barr virus. (14 refs)

78-6458 **Translocation of a Hydrocarbon Fluorescent Probe Between Epstein-Barr Virus and Lymphoid Cells: An Assay for Early Events in Viral Infection.** (Eng) Rosenthal, K. S. (Harvard Medical Sch., Boston, MA, 02115); Yanovich, S.; Inbar, M.; Strominger, J. L. *Proc Natl Acad Sci USA* 75(10): 5076-5080; 1978.

An assay to determine early biochemical events during cell-virus interactions is described, as well as its application in measuring events following the interaction of Epstein-Barr virus (EBV) with different types of lymphoid cells. The method is based on translocation of the hydrocarbon fluorescent probe diphenylhexatriene (DPH) between viral envelopes and cellular membranes, as monitored by fluorescence polarization (P) analysis. Using a model system, the high P value (0.324) of DPH-labeled cholesterol/phosphatidylcholine liposomes and the low P value (0.157) of DPH-labeled phosphatidylcholine liposomes allowed detection of DPH-translocation between interacting liposomes. This was monitored by the change in P in either direction. The P value of DPH-labeled EBV was significantly higher (p.350-0.392) than the P value of DPH-labeled lymphoid cells (0.238-0.289). Hence, DPH translocation could be detected by changes in P following incubation of DPH-labeled EBV and nonlabeled cells. A marked decrease in P was observed after incubation of DPH-labeled EBV with nonlabeled lymphoblastoid Raji cells or fresh human B lymphocytes. However, only a slight decrease in P was obtained when DPH-labeled EBV was incubated with nonlabeled fresh human T lymphocytes or fresh rabbit T or B lymphocytes. Moreover, incubation of human B lymphocytes with purified complement 3 (a putative inhibitor for the EBV receptor) prior to the addition of DPH-labeled EBV abolished the decrease in the P value. Most of these experiments were carried out with both the P3HR-1 and B95-8 EBV strains. Therefore, DPH translocation, as determined by fluorescence polarization, measures some early event during interaction of this enveloped virus and mammalian cells. The potential applicability of this technique to other viruses is illustrated by an experiment with Semliki Forest virus. (32 refs)

78-6459 **An Evaluation of Antibody Titers to the Epstein-Barr Virus as a Test for Susceptibility to Cancer.** (Eng) Levine, P. H. (Lab. Viral Carcinogenesis, NCI, NIH, Bethesda, MD, 20014); Connelly, R.; Heath, C. W.; Caldwell, G. G.; Terasaki, P. I.; Mickey, M. R.; Fabrizio, P. *In: Prevention and Detection of Cancer. Proceedings of the Third International Symposium on Detection and Prevention of Cancer Held by the International Study Group for the Detection and Prevention of Cancer in New York, April 26 - May 1, 1976.* International Study Group for the Detection and Prevention of Cancer. (New York, NY): Vol. 2 (part 1), 2 pp.; 1525-1537; 1978.

Antibodies to Epstein-Barr virus (EBV) capsid anti (VCA) were studied in 210 normal first-degree relative cancer patients from 31 families with multiple cancer c (MCF). Sera from each relative were matched by age, and sex to a control sample from a normal individual were tested for VCA antibodies by immunofluorescenc a procedure using P3HR-1 antigen and Hyland goat anti man IgG as antisera. VCA titers were significantly highe normal MCF relatives compared with controls, which gest that EBV-VCA titers may be indicative of an abnorm ity predisposing to malignancy. A comparison of EBV-V titers and histocompatibility antigens HL-A among patie with Hodgkin's disease or Burkitt's lymphoma and their r tives showed that high titers were not associated with specific HL-A types (A-1, B-5, B-8) linked to lymphoproli ative disease. (27 refs)

78-6460 **Papain Solubilization of the Epstein-B Virus-induced Membrane Antigen.** (Eng) Pe son, G. R. (Dept. Microbiology, Mayo Clinic/Foundati Rochester, MN, 55901); Qualtiere, L. F. *J Virol* 28 344-351; 1978.

Epstein-Barr virus (EBV)-induced membrane antigen (M was purified and characterized in a series of experimer EBV-infected Raji cells were exposed to papain (5 to units/1 x 10^7 to 2 x 10^7 cells) for 1 hr. Membrane immu fluorescence and antibody-dependent cellular cytotoxic (ADCC) assays of the cells revealed that most of the MA v removed by this treatment. Soluble MA was demonstrat in papain digests through inhibition of ADCC and by inhi tion of the binding of anti-MA antibodies to EBV-infect Raji cells, as detected with the use of ^{125}I-labeled staphyloc cal protein A. Papain extracts were centrifuged at 100,0 x*g* for 1 hr and tested for MA activity in the ^{125}I-prote A test. Approx 75% of this activity remained in the supern tant, indicating that most EBV MA activity in the extra was associated with low-mol-wt material. Antiserum p pared from an owl monkey immunized with the papain e tracts had no detectable antibodies to viral capsid antigen early antigen; however, an antibody reactive to EBV-induc MA was present at a titer of 80 and a neutralization titer 320. (23 refs)

78-6461 **Isolation of Epstein-Barr Virus (EBV) in Su pensions of Cells Obtained from Patients wi Different Hemoblastoses.** (Rus) Agrba, V. Z. (Inst. Exper mental Pathology and Therapy, Acad. Medical Scienc USSR, Moscow, USSR); Iakovleva, L. A.; Lapin, B. A Lebedev, V. N.; Grigor'ev, A. S.; Sangulia, I. A.; Timano skaya, V. V.; Chuvirov, G. N.; Bukaeva, I. A.; Markova,

Markarian, D. S.; Kokosha, L. V. *Vopr Onkol* 24(9): 0; 1978.

ension cultures prepared from peripheral blood lym-cytes of leukemia patients and from lymph node cells and en cells from patients with other hemoblastoses were in-gated electron microscopically for the presence of Ep--Barr virus (EBV). Eight virus-producing cell lines were olished: 5 from 7 patients with myelogenous leukemia, om 9 patients with lymphogranulomatosis, and 1 from a ent with a lung tumor and a leukemoid reaction. No s-producing cell lines could be established from three pa-s with lymphocytic leukemia or from another patient non-Hodgkin's lymphoma. All eight cell lines produced in 0.5%-3% of the cells. The cells of the virus-produc-lines were lymphoblasts with B-cell characteristics. (34

6462 **Further Studies on the Replication of Adenovirus Type 2 DNA.** (Eng) Raptis, L. (Departement Microbiologie, Faculte de Medecine, Centre Hospitalier versitaire, Universite de Sherbrooke, Sherbrooke, Que-Canada J1H 5N4); Delbecchi, L.; Bourgaux, P. *Can J hem* 56(9): 857-865; 1978.

distribution of ^{3}H-thymidine in pulse-labeled replicating adenovirus 2 (Ad2) DNA was determined, and an at-pt was made to pinpoint the origin(s) of replication on Ad2 genome. Monolayer cultures of Ad2-infected KB s were subjected to short pulses of ^{3}H-thymidine at the e of max viral DNA synthesis. Nascent viral DNA was acted from the cells, purified, and fractionated into partly completed (C) molecules. The latter were cleaved by *Eco* *Hin*dIII, *Hpa*I, or by *Hin*dIII + *Hpa*I, and the fragments e separated electrophoretically. R molecules were also ted with these enzymes, but the double-stranded frag-nts were separated from the partly single-stranded frag-nts by chromatography on benzoylated-naphthoylated hylaminoethylcellulose before they were subjected to trophoresis. Analysis of C molecules revealed a strong ferential labeling of fragments derived from the ends of molecules, as expected if both ends contain termini for ication. Analysis of double-stranded fragments from R ecules revealed a predominant labeling of the center of genome that could be reconciled with initiation occurring trally or at both ends. In addition, two gradients of label-rising toward each end and encompassing the outer quar-of the molecule, were noted that slowly receded when pulse length was increased. This finding may reflect an rrepresentation of molecules in the late stages of replica-in the pool of nascent DNA, and it is to be expected if lication slows down when it nears the termination site(s). s interpretation is consistent with the labeling kinetics of various portions of the genome observed in the pool of nolecules. Because of this complication, however, the dis-ution of label in R molecules cannot be used to determine the exact location of the origin(s) of replication on the Ad2 DNA. (20 refs)

78-6463 **Size Distribution of Polyadenylated Adenovirus 2 RNA Synthesized in Isolated Nuclei.** (Eng) Zimmer, S. G. (Dept. Pathology, Univ. Kentucky Medical Center, MDRF 3, Lexington, KY, 40506); Goldenberg, C. J.; Carlson, D. P.; Craig, E. A.; Raskas, H. J. *Biochemistry* 17(20): 4207-4213; 1978.

Nuclei isolated from cultures of KB cells 14 hr after infection with adenovirus 2 were studied for their ability to transcribe viral RNA with fidelity and to generate discrete viral RNA size classes from specific regions of the genome. RNA synthesized in vitro was approx 40% viral and was derived almost entirely (95%) from the viral *r* strand. Hybridization-inhibition experiments demonstrated that the in vitro RNA transcripts included two classes of sequences, those restricted to the nucleus in vivo and those in cytoplasmic RNA. Quantitation of viral sequences from defined regions of the genome was performed by exhaustive hybridization with seven viral DNA fragments generated by digestion with endonuclease R-*Eco*R1 or R-*Sma*I. The sizes of the viral RNA synthesized by the KB cell nuclei in vitro were compared with viral RNA labeled by in vivo experiments (whole cell cultures). The polyadenylated viral RNA synthesized in vitro ranged in size from 13S to 28S, with peaks of 28S, 25S, and 22S. The polyadenylated nuclear RNA labeled during a 30-min in vivo pulse was larger, 23S-36S; however, incubation of the prelabeled nuclei in RNA synthesis conditions resulted in a gradual decrease in the size of the prelabeled RNA. RNA prelabeled in vivo contained 36S, 28S, and 22S species that, when incubated under in vitro conditions, were converted to a size distribution identical to that of RNA synthesized by isolated KB nuclei under in vitro conditions. This evidence supports the view that the in vivo and in vitro syntheses of RNA are identical. (46 refs)

78-6464 **Biochemical Studies on Bovine Adenovirus Type 3. IV. Transformation by Viral DNA and DNA Fragments.** (Eng) Igarashi, K. (Biological Res. Labs., Central Res. Div., Takeda Chemical Industries, Ltd., Osaka, Japan); Sasada, R.; Kurokawa, T.; Niiyama, Y.; Tsukamoto, K.; Sugino, Y. *J Virol* 28(1): 219-226; 1978.

Using the calcium technique, mouse cell line A31 (a clone of line BALB/3T3) was transformed in vitro with intact DNA of bovine adenovirus type 3 (BAV3) and also with BAV3 DNA fragments produced by two specific restriction endonucleases. Approx 5 to 10 foci/μg of DNA were produced within 20 days of transformation by BAV3 DNA. All foci were composed of round, cuboidal, and densely packed cells. RNase A and Pronase had little effect on the transformation, but DNase was able to abolish it completely. The *Eco* RI fragment D, mapping at 3.6 to 19.7 units, could transform

A31 cells almost as efficiently as intact DNA. No transformation occurred with *Hin*dIII fragments J, E, and B, but enzymatic joining of J + E (0-11.9 map units) with a ligase restored transforming activity. These results indicate that the genetic information of BAV3 necessary for transformation is located between map units 3.6 and 11.9, comprising 8.3% of the viral genome. Cells transformed by BAV3 DNA, BAV3 DNA *Eco*RI fragment D, and BAV3 *Hin*dIII fragment J+E (lines Tr, TrD, and TrJE, respectively) all showed the positive nuclear immunofluorescence characteristic of BAV3-transformed cells. Compared with untransformed A31 cells, all transformed lines tested showed rapid growth, high saturation density, and anchorage-independent growth. They also contained BAV3-specific tumor antigen. Lines Tr and TrD produced tumors in 100% of nude mice injected in 2 wk, and all three transformed lines produced tumors in 63%-100% of BALB/c mice within 2 mo. (23 refs)

78-6465 **Biochemical Studies on Bovine Adenovirus Type 3. III Cleavage Maps of Viral DNA by Restriction Endonucleases *Eco*RI, *Bam*HI, and *Hin*dIII.** (Eng) Kurokawa, T. (Biological Res. Labs., Central Res. Div., Takeda Chemical Industries, Ltd., Osaka, Japan); Igarashi, K.; Sugino, Y. *J Virol* 28(1): 212-218; 1978.

The restriction endonucleases *Eco* RI, *Bam* and *Hin*dIII were used to construct cleavage maps of bovine adenovirus type 3 (BAV3) DNA by analyzing overlapping sets of specific fragments produced by the enzymes and by cleavage of DNA previously end-labeled by T4 DNA polymerase. After digestion, fragments were analyzed by gel electrophoresis. *Bam*HI yielded 5 fragments (A-E); *Eco*RI, 7 (A-G); and *Hin*dIII, 12 (A-L). The order of fragments on the the DNA molecule was determined by overlapping the specific fragments produced by two different restriction endonucleases. The order was GDACBFE for the *Eco*RI fragments, AEBDC for the *Bam* HI fragments, and JEBKACDHFGIL for the *Hin*dIII fragments. The BAV3 preparation contains a unique population of incomplete virus whose genome has a deletion of 13% of the complete virus genome. Restriction endonuclease digestion of the incomplete virus DNA revealed that *Eco*RI E and F, *Bam*HI C, and *Hin*dIII G, I, and L fragments were missing. Therefore, the deleted region of incomplete virus DNA is located near the right end of complete virus DNA, a result consistent with previous electron microscope observations of heteroduplex molecules formed between complete and incomplete BAV3 DNA. (22 refs)

78-6466 **Transcription of Viral Sequences in Cells Transformed by Adenovirus Type 5.** (Eng) Frolova, E. I. (Inst. Molecular Biology, Acad. Sciences USSR, Moscow, USSR); Zalmanzon, E. S. *Virology* 89(2): 347-359; 1978.

Viral genomes and their transcription and chromatin conformation were studied in five lines of adenovirus 5 (Ad5)-transformed rat embryo cells. Renaturation experiments sh that all lines contained sequences homologous to *Hpa* ment E, but they varied in other Ad5 DNA sequences. any viral functions required for maintaining the transf phenotype are encoded by the left end of Ad5 DNA. A all viral DNA sequences in the three lines studied were scribed into nuclear RNA. Only part of the sequences c I fragment E in all lines were sensitive to DNase I. (2

78-6467 **The Relationship Between T Antigens of group A and B Adenoviruses.** (Eng) Shiro (Inst. Medical Science, Univ. Tokyo, Shiroka Minato-ku, Tokyo 108, Japan); Shimojo, H.; Sekikaw Fujinaga, K. *Virology* 89(2): 627-631; 1978.

The relationship between the tumor antigens (TAg's) o groups A and B adenoviruses was investigated by in immunofluorescence and DNA-DNA hybridization e ments. Secondary cultures of human embryo kidney cel 3Y1 cells (a line derived from a Fischer rat embryo) infected with adenovirus 12 (Ad12), Ad31, Ad7, Ad3, and Ad5 (10 plaque-forming units/cell) in the presence μg/ml of cytosine arabinoside. After 24 hr, cells were vested and stained by indirect immunofluorescence with of rats bearing GY1 cell (rat line transformed by the dIII-G fragment of Ad12 DNA) tumors. T Ag with the phology of cytoplasmic flecks and nuclear fibrils wa served in Ad12- and Ad31-infected cells, but T Ag pre nantly in the form of nuclear fibrils was observed in Ad7 Ad3-infected cells. Thus, the morphology of T Ag see be determined by virus type. T Ag was not detected in and Ad5-infected cells. These observations indicate that is common among members of subgroups A (Ad12, A and B (Ad7, Ad3) adenoviruses, a conclusion that agrees the high homology between the *Hin*dIII-G fragment of DNA and Ad31 DNA and with the high homology bet the *Hin*dIII-IJ fragment of Ad7 DNA and Ad3 DN addition, T Ag of Ad7 was partially stained by imm fluorescence with antiserum to Ad12 T Ag and vice v However, the homology between the transforming fragn of Ad12 DNA and Ad7 DNA was only 9%-15%. The crepancy between the common antigenicity and I homology, which also occurs with simian virus 40 and virus, is discussed. (9 refs)

78-6468 **Adenovirus-induced Changes in the Weig the Mouse Spleen and Thymus.** (Rus) Agee A. I. (Lab. Virology, P. A. Hertsen Res. Inst. Oncology, cow, USSR); Erkhov, V. S.; Sviridova, I. K. *Biull Eksp Med* 86(9): 356-358; 1978.

In an attempt to detect lymphoid cells with increased pr erative potential, newborn CBA mice were inoculated simian adenovirus (SA7, C8, 10^{-4} units/0.1 ml). Twenty days later, the mice were sacrificed and the spleen cells

nsferred into newborn syngeneic mice (9 x 10^6 s/mouse). The effect of the transfer was measured changes in the wt of the lymphoid organs in 10-day- mice. The transfer of splenocytes from mice during latent period of SA7-induced carcinogenesis result- in a significant increase in the spleen wt:body wt o (5.64, compared with 3.71 after transfer of normal enocytes and 3.72 in controls) and significant de- ase in the thymus wt:body wt ratio (4.04, vs 4.88 6.21, respectively). Thus, adenoviral carcinogenesis some manifestations of autoimmune disease. (10)

6469 **Transcription Map for Adenovirus Type 12 DNA.** (Eng) Smiley, J. R. (Dept. Therapeutic liology, Radiology Labs., Yale Univ. Sch. Medicine, New ven, CT, 06510); Mak, S. *J Virol* 28(1): 227-239; 1978.

physical locations and strand derivation of the adenovi- type 12 (Ad12) DNA sequences expressed as early and cytoplasmic RNA (cyRNA) were mapped, and the rela- rates of accumulation of this RNA from different regions he genome were monitored at different times after infec- . ^{3}H-labeled, intact, complementary l- and r-strand DNA uences were hybridized with saturating amounts of unla- d late cyRNA extracted 24 hr after infection of human cells with Ad12. The segments of each DNA strand com- nentary to the RNA were then purified by S1 nuclease stion of the hybrids. These ^{3}H-DNA preparations were d as templates for hybridization with unlabeled DNA ments generated by the restriction endonucleases *Eco*RI, mHI, and *Hin*dIII. The completed map was very similar hat of Ad2. The subset of the late cyRNA sequences that expressed at early times was located on the map by hybri- ng labeled, early cyRNA to both unlabeled DNA frag- nts and unlabeled complementary strands of specific frag- nts. Early cyRNA hybridized to the r strand of *Eco*RI-C *Bam*HI-B and to the l strand of *Bam*HI-E. Hybridization *Bam*HI-C was also observed. The relative rates of accumu- on of cyRNA complementary to individual restriction ments was measured at both early and late times. Early ing infection, most of the viral RNA appearing in the oplasm was derived from the molecular ends of the ome. Later (24-26 hr postinfection), most of the newly led cyRNA was transcribed from DNA sequences map- g between 25 and 60 map units on the genome. (39 refs)

6470 **Morphological Revertants of Adenovirus Type 12-Transformed Hamster Cells.** (Eng) Grone- g, J. (Inst. Genetics, Univ. Cologne, Cologne, W. many); Sutter, D.; Soboll, H.; Doerfler, W. *J Gen ol* 40(3): 635-645; 1978.

B_3 subline of baby hamster kidney (BHK21) cells, the (T637) derived by transformation of this subline with novirus type 12, and two morphological revertants of 7 (F10 and G12) were characterized. In contrast to T637 cells, which were round, the revertant lines exhibited a fibroblastic morphology, as did B_3 cells. Unlike B_3 and T637 cells, the revertant cells reacted with anti-LETS (large, external, transformation-sensitive protein) serum. The revertants were also less easily agglutinable by concanavalin A and less likely to form colonies in soft agar than T637, and they resembled B_3 in their uptake of amino acids and 2-deoxyglucose. Judging from the time required to induce tumor growth, G12 and F10 grew less readily in 4-wk-old Syrian hamsters than B_3 and T637 cells. The karyotypes of the four cell lines appeared to be indistinguishable, but the patterns of integrated virus genomes in the revertants differed markedly from that of T637 cells; F10 appeared to have lost all viral DNA sequences. (22 refs)

78-6471 **Activated Endogenous Viruses of Tumor Induced by Human Adenovirus: An Electron Microscope Study.** (Eng) Ohmori, M. (Dept. Pathology, Okayama Univ. Medical Sch., Okayama 700, Japan). *Exp Mol Pathol* 29(2): 260-271; 1978.

Activated endogenous C-type virus particles (ECP) and intracisternal A particles (IAP) in C3H/BifB mice tumors induced by human adenovirus 12 (Ad12) were studied by electron microscope freeze-fracture-etching techniques.IAP were found in the endoplasmic reticulum (ER) and perinuclear cisternae. The ER membrane was electron dense and protruded into the cisternae to form either a single particle or many particles that were released eventually into the cisternae. The ECP particles began as spherical elevations on the tumor cell membrane; as the particles matured, the surface projections were lost and the particles became polygonal in shape. The production of ECP appeared to be continuous at some cell sites. Because these particles are not seen in chemically induced or in spontaneous tumors of syngeneic mice, it is assumed that Ad12 infection supplies the incomplete, masked genome of an endogenous leukemia virus with the material needed for its proliferation. (31 refs)

78-6472 **Nucleotide Sequence Relationship Between Intracisternal Type A Particles of *Mus musculus* and an Endogenous Retrovirus (M432) of *Mus cervicolor.*** (Eng) Kuff, E. L. (Lab. Biochemistry, NCI, NIH, Bethesda, MD, 20014); Lueders, K. K.; Scolnick, E. M. *J Virol* 28(1): 66-74; 1978.

The purified high-mol-wt RNA of *Mus musculus* (MM) intracisternal A-type particles was tested for homology with the viral genome of M432, a retrovirus isolated from *M. cervicolor* (MC). Partial nucleotide sequence homology was observed between the 32S and 35S RNA components of A-type particles from neuroblastoma cell line N4 (from a tumor in A/Jax mice) and the 70S fraction from M432. M432 complementary DNA (cDNA) was hybridized to about the same extent (25%-30% of the homologous reaction) by MM cellular

DNA and A-particle RNA; therefore, the entire group of M432-related MM sequences could be represented in the A-particle RNA. The hybrids showed a lower thermal stability than those formed with homologous RNA. The reaction was commensurate with that found between M432 cDNA and divergent sequences in the MM genome. The capacity to hybridize M432 cDNA was correlated closely with the concentration of A-particle sequences in the cytoplasmic RNA of several MM cell types. The major RNA fraction of M432 virus showed a reciprocal partial reaction with the A-particle cDNA's; the virus, which was grown in NIH/3T3 (MM) cells, also contained a small proportion of apparently authentic A-particle nucleotide sequences. However, a portion of the A-particle sequences, the so-called abundant class, seemed to be lacking in M432 genomic RNA. Multiple copies of both M432- and A-particle-related sequences were also present in MC DNA. However, the latter seemed to contain a more complete representation of the intracisternal A-particle information than was found in the M432 virus, since A-particle 35S cDNA was hybridized to a greater extent by MC cellular DNA than would have been expected on the basis of its partial homology with M432 viral RNA, and sequences homologous to the A-particle abundant-class probe were present in the DNA, even though they had no counterpart in the M432 viral genome. (31 refs)

78-6473 **Defective C-type Retrovirus Particles Secreted by L1210 Leukemia Cells.** (Eng) Kennel, S. J. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830); Tsakeres, F.; Kelly, P. A.; Allison, D. P. *Cancer Res* 38(12): 4574-4579; 1978.

C-type retrovirus particles released from cultures of 1210 leukemia cells (L1210) were characterized as a first step in determining the effect virus may have on the biology of the L1210 model system. The virus particle was found to be nononcogenic and noninfectious in standard assays for xenotropic and ecotropic murine retroviruses. This L1210 virus had a normal complement of viral proteins except that it had no detectable glycoprotein with a mol wt of 70,000 (gp70). Quantitative radioimmunoassay for the major structural protein, the one with a mol wt of 30,000 (p30), indicated that the virus is at least a thousandfold more defective than ecotropic viruses such as AKR and Moloney leukemia virus. L1210 cells grown in vitro released about 20 times more particle-associated p30 than in vivo-cultured cells, but cell-associated p30 and gp70 were found at similar levels. Both in vitro- and in vivo-cultured cells displayed gp70 on their surfaces that appeared to be of higher mol wt than the gp70 from most ecotropic viruses. Cells grown in vitro released a high level of non-virion-associated gp70 into the growth medium, but the high concentration of gp70 in the serum of normal DBA/2 mice precluded such measurements on in vivo-cultured cells. These results indicate that L1210 virus does not act as a classical infectious leukemia virus during the growth of L1210 cells, but the presence of relatively large amounts of viral antigens in these cells may affect the immune response to them. (28 refs)

78-6474 **The Etiology of Laryngeal Papillomat** (Eng) Quick, C. A. (Div. Otolaryngology, V Virginia Medical Center, Morgantown, WV, 26506); Fa A.; Krzysek, R. *Laryngoscope* 88(11): 1789-1795; 1978.

Virological techniques for isolating whole virus, free DNA, or integrated viral DNA were used to deter whether the virus involved in the etiology of laryngeal p lomatosis is human papilloma virus. Human papilloma v banded at 1.34 g/ml in a cesium chloride gradient; exam tion of the supernatant from pooled laryngeal papill specimens showed no such band, indicating that no wh virus was present. The electrophoretic mobility of the su natant from a cutaneous wart was compared with tha markers of known molecular size, and the results were p tive for free human papillomatosis virus DNA. When technique was repeated with laryngeal papillomas, no c band was identifiable in the agarose gel. When integra DNA was assayed by molecular hybridization, human pa loma virus type V showed 100% hybridization, but no bridization was seen with the laryngeal papillomas. The sults suggest that the virus responsible for laryn papillomatosis is not the same as the virus responsible cutaneous papillomatosis lesions and, for the most part, ex in integrated DNA form. (7 refs)

78-6475 **Interactions of Shope Papilloma Virus Some Other DNA Viruses.** (Eng) Chardon Y. (Unite de Virologie Fondamentale et Appliquee, SERM, Groupe de Recherche 33, CNRS, 1, place du Pro seur Joseph-Renaut, F 69371 Lyon Cedex 2, France); Gre land, T.; Lyon, M.; Sohier, R. *Bull Cancer (Paris)* 65 195-206; 1978.

The interactions of Shope papilloma virus (SPV) with mate and rabbit cells in tissue culture were investigated. rabbit cell cultures were derived from normal epider SPV-infected epidermis, SPV-induced papillomas, and SPV-associated carcinoma. None of these cell cultu whether infected in vitro with SPV or derived from tiss infected in vivo, produced infectious SPV or detectable v antigens. Some other DNA viruses behaved differently cells that had been in previous contact with SPV either vitro or in vivo. Adenovirus type 5 multiplied better in hun cells infected 24 hr previously with SPV than in untrea controls. The production of infectious virions of herpes s plex virus or Shope fibroma virus was reduced in cells deri from SPV-induced papillomas or carcinoma, due to a de in viral maturation. Of the rabbit cells, only those deri from in vivo infected tissue or those previously infected vitro with SPV were transformed by simian virus 40. rabbit cell lines derived from papillomas or carcinoma fered from their counterparts derived from normal epider or from tissue infected 24 hr before biopsy in their karyot and in their ability to grow in soft agar. Similar karyoty alterations were induced in cells derived from healthy epi mis by infection in vitro with SPV. (29 refs)

476 **Heterogeneity of Human Papilloma Viruses.** (Eng) Pfister, H. (Institut fur Virologie, Zen- fur Hygiene, Hermann-Herder-Strasse 11, 7800 Frei- W. Germany); Gissmann, L. *Bull Cancer (Paris)* 65(2): 67; 1978.

types of human papillomaviruses, HPV-1 and HPV-4, characterized by purifying virions from single skin . Viral DNA was extracted by solubilizing the protein with sodium dodecyl sulfate and then cleaved with dif- t restriction endonucleases. The resulting fragments separated by gel electrophoresis. The results show no onship between HPV-1 and HPV-4 as far as the follow- riteria are concerned: the pattern of restriction enzyme ients of their DNA, DNA-complementary RNA hy- zation, and complement fixation with specific rabbit an- . Moreover, the mol wts of their major proteins differed ficantly. Both virus types could be isolated from plantar and from verrucae vulgares. In addition, a third type PV was isolated from the skin warts, with HPV-1 or with -4 rabbit antiserum. (10 refs)

477 ***Mastomys natalensis* Papilloma Virus (MnPV), the Causative Agent of Epithelial Prolifera- : Characterization of the Virus Particle.** (Eng) Muller, nstitut fur Virologie, Justus-Liebig-Universitat Giessen, kfurter Strasse 107, 6300 Lahn-Giessen, W. Germany); mann, L. *J Gen Virol* 41(2): 315-323; 1978.

physicochemical and morphological characteristics of *omys natalensis* papilloma virus (MnPV) were studied. s particles banded in CsCl gradients at densities of 1.34 (full particles) and 1.29 g/ml (empty particles). The DNA had a bouyant density of 1.7104 g/ml, and it ed in three different conformations (supercoiled circular, ed circular, and linear). The sedimentation values of three conformations were 23S-24S, 16S-17S, and 15S, respectively. Although the mol wt of MnPV DNA x 10^6) was similar to that of human papilloma virus V) I DNA, the size of the fragments obtained after cleav- of MnPV DNA with the restriction endonuclease *Hae* iffered from that of HPV cleavage fragments. Polya- mide gel electrophoresis showed that virion contained ifferent polypeptides; the major structural protein had l wt of 56,000. Skin tumors were induced in 36% of als infected with purified MnPV (containing approx 150 nl of virus protein), but no cutaneous alterations were rved when the particles were inoculated in the presence nti-MnPV serum; this indicated that MnPV was the eti- c agent in the skin proliferations. MnPV was reisolated the experimental tumors. (22 refs)

478 **Conditions Leading to the Establishment of the N (*a* Gene Dependent) and A (*a* Gene Independ- Transformed States after Polyoma Virus Infection of Rab Fibroblasts.** (Eng) Rassoulzadegan, M. (Centre de Biochimie, Universite de Nice, 06034 Nice, France); Seif, R.; Cuzin, F. *J Virol* 28(2): 421-426; 1978.

Infection of normal rat fibroblasts (FR 3T3) with the early temperature-sensitive mutant (*tsa*) of polyoma virus was shown to lead to either the A or the N phenotype. The choice between A and N was made during the first 5 days at 33 C and primarily depended on the growth potential of the infected cells during that time period. Polyoma *tsa*-transformed A clones were temperature-independent for expression of the transformed phenotype, but N transformants were strongly temperature-dependent. The crucial parameter in the N vs A choice is probably the physiological state of the cells during the early part of transformation, and it is likely that no causal relationship exists between the method of selection and the subsequent mode of maintenance. A transformation occurred in both liquid and agar media when the infected cells were maintained under growth-restricting conditions, such as absence of anchorage and contact inhibition at confluency. N transformation occurred in cells maintained in active growth after virus infection (sparse cultures on a solid substratum). The N and A states were redefined as meaning polyoma *a* gene (or simian virus 40 *A* gene) dependent vs independent for maintenance of the transformed state. (12 refs)

78-6479 **Tumor Antigens Induced by Nontransforming Mutants of Polyoma Virus.** (Eng) Silver, J. (Dept. Hematology, Beth Israel Hosp., Boston, MA, 02115); Schaffhausen, B.; Benjamin, T. *Cell* 15(2): 485-496; 1978.

Wild-type polyoma virus and nine independently isolated hr-t mutants of polyoma virus (with an absolute defect in transformation) were studied to determine which tumor (T) antigens they induced during lytic infection in mouse cells. In a variety of cell lines, wild-type virus induced a major T-antigen species with an apparent mol wt of 100,000 daltons and four min or T-antigen species with apparent mol wts of 63,500, 56,000, 36,000, and 22,000 daltons. The hr-t mutants induced a normal 100,000-dalton T antigen but none of the minor wild-type virus species; it did induce antigens with mol wts of 6,000-9,000 daltons. "Point" hr-t mutants induced normal amounts of the 56,000-dalton antigen and reduced amounts of the 22,000-dalton antigen but neither of the other two minor antigens. Ts-a mutants, which have a temperature-sensitive defect in ability to induce stable transformation induced T antigens with the same mobility as wild-type virus, but the 100,000-dalton species was thermolabile compared with the wild-type species. A double mutant virus carrying both a ts-a mutation and a deletion hr-t mutation induced a thermolabile 100,000-dalton antigen but none of the minor species. Cell fractionation studies with productively infected cells were carried out to localize the T-antigen species. (55 refs)

78-6480 **Contact Behaviour and Pattern Formation of BHK and Polyoma Virus-transformed BHK Fi-**

broblasts in Culture. (Eng) Erickson, C. A. (Dept. Biology, Yale Univ., New Haven, CT, 06520). *J Cell Sci* 33: 53-84; 1978.

The contact behavior of normal (BHK21/13) and polyoma virus-transformed (BHK21) cell lines was studied using high-resolution, time-lapse cinemicrography combined with scanning electron microscopy. At high density, the BHK21/13 cells were generally organized in monolayered parallel arrays with little crisscrossing of whole cells, whereas the BHK21 cells showed a multilayered, highly crisscrossed arrangement with considerable nuclear overlap. In both cell lines, ruffling was inhibited when contact was made ruffle to ruffle. When BHK21/13 cells contacted each other ruffle to side, strong adhesions occurred with accompanying paralysis of ruffling. Then the contacting cell either changed direction, usually spreading along the side of the contacted cell, or it occasionally continued to protrude and underlap the other cell, although the original adhesions remained. The transformed cells never formed strong ruffle-to-side adhesions, and they usually underlapped each other totally. None of the cells moved over the surface of others (overlapping), and all crisscrossing occurred by underlapping. The BHK21 cells had many fewer side-to-substratum adhesions than the BHK21/13 cells, which could explain the ease with which the transformed cells underlap. (36 refs)

78-6481 **Growth Factors Produced by Sarcoma Virus-transformed Cells.** (Eng) Todaro, G. J. (Lab. Viral Carcinogenesis, NCI, NIH, Bethesda, MD, 20014); De Larco, J. E. *Cancer Res* 38(11, part 2): 4147-4154; 1978.

The epidermal growth factor (EGF) binding capacity of a variety of normal and transformed cell lines was determined. Simian virus 40 (SV40), polyoma virus, and avian sarcoma virus transformants showed normal levels of EGF binding. Only 5/47 chemically transformed cells had lost their EGF specific receptors. However, the binding levels of all murine sarcoma virus (MSV)-transformed lines tested (mouse, rat, and mink) were altered; in none of the cases was multiplication-stimulating activity (MSA) binding reduced. Thus, loss of EGF receptors after transformation appears to be specifically associated with sarcoma virus transformation. Of the >40 human fibrosarcomas tested, 2 had normal levels of EGF receptors but no MSA receptors. One of the MSA receptor-negative lines was producing a family of related growth polypeptides that interacted with MSA receptors but not with EGF receptors and stimulated cell division in cells of various species. The activities of both the sarcoma growth factor and the MSA-related human fibrosarcoma growth factor were heat-stable, protease-sensitive, and sensitive to disulfide-reducing agents. It appears that the production of the sarcoma growth factor is at least in part the mechanism by which sarcoma viruses transform fibroblasts. One of the ways in which cells become transformed may be by endogenous production of growth factors for which they have receptors and to which they are capable of responding. This in production of growth polypeptides serves as a constant st lus for cell division, thereby releasing these cells from of the normal physiological controls. (29 refs)

78-6482 **Replication of Polyoma DNA in Isolated clei. Synthesis and Distribution of Ini** RNA. (Eng) Eliasson, R. (Medical Nobel Inst., Biochemistry, Karolinska Inst., Stockholm, Swe Reichard, P. *J Biol Chem* 253(20): 7469-7475;

The synthesis and distribution of initiator RNA (iRNA) studied in nuclei isolated from polyoma virus-infected mouse fibroblasts. The nuclei were incubated for 5 min C under standard conditions, including 2 mM ATP ^{14}C-dATP, ^{3}H-guanosine triphosphate (^{3}H-GTP), an ^{32}P-GTP. Polyoma DNA was extracted selectively, an plicative intermediates (RI) and iRNA were purified measured. The frequency with which ATP or GTP was to start iRNA synthesis depended on the ATP/GTP during incubation. The total number of 5′-ends of iRN most equalled the total number of 3′-ends, indicating most iRNA molecules are complete. Newly synthe iRNA attached to short Okazaki fragments was first det at 1.5 min. Between 1.5 and 5 min, iRNA accumulated longer strands, but little change occurred after 5 min. times (1.5, 5, 10, and 15 min), there was an unexplaine cumulation of iRNA linked to very short strands (25-3 cleotides in length). Only one-fourth to one-third Okazaki fragments contained iRNA. This value wa dependent of the length of the strands (270 or 95 nucleo or incubation time. Since the uniqueness of iRNA is size, not its nucleotide sequence, it is unlikely that a sp base sequence of the template determines either the begi or the end of iRNA synthesis. It is suggested that iR serves as a primer for the synthesis of Okazaki fragment that it is transcribed randomly on the genome during replication. (32 refs)

78-6483 **Polyoma Virus Giant RNAs Contain Ta Repeats of the Nucleotide Sequence of th tire Viral Genome.** (Eng) Acheson, N. H. (Swiss Inst. Ex mental Cancer Res., 1066 Epalinges, Switzerland). *Proc Acad Sci USA* 75(10): 4754-4758; 1978.

The arrangement of viral nucleotide sequences in the late virus-specific RNA's synthesized in polyoma viru fected mouse cells was studied by electron microscopy o brids between purified high-mol-wt viral RNA and the II-1 fragment of polyoma DNA, which contains 91% o viral genome. Hybrid molecules containing a short gle-stranded gap (corresponding to the 9% of viral seque not present in *Hind*II-1), flanked by double-stranded reg were photographed and measured. Most hybrid mole

tained no single-stranded loops or branches, demonstrat- that all viral sequences are transcribed contiguously and t no nonviral sequences are present in the RNA. In hybrid lecules containing RNA up to 3.5 times the genome gth, a repeating structure of single-stranded gaps 8% of genome length was observed interspersed with dou- stranded regions 89% of the genome length; therefore nt polyoma RNA's contain tandem repeats of the leotide sequence of the entire viral DNA. A small propor- n of hybrid molecules contained single-stranded branches deletion loops in characteristic positions, indicating that IA splicing may occur on high-mol-wt nuclear polyoma IA. (29 refs)

6484 **Characterization of the mRNA's for the Polyoma Virus Capsid Proteins VP1, VP2, and VP3.** ng) Hunter, T. (Tumor Virology Lab., Salk Inst., San ego, CA, 92112); Gibson, W. *J Virol* 28(1): 240-253; 1978.

e polyoma virus capsid proteins VP1, VP2, and VP3 of d-type polyoma virus were identified following translation otal cytoplasmic RNA in the wheat germ system in the sence of ^{35}S-methionine. Upon sodium dodecyl sul- e-polyacrylamide gel electrophoresis, bands corresponding the three capsid proteins were evident. The bands were ent from analyses of mock infected cultures. The transla- n products of RNA selected from total cytoplasmic RNA infected cells by hybridization to polyoma virus DNA wed a high degree of enrichment for VP1, VP2, and VP3. ctionation of this virus-specific RNA showed that almost VP1 messenger RNA (mRNA) activity contains poly-A that a substantial proportion of VP2 and VP3 mRNA ivity is poly-A deficient. Further proof of the identity of se proteins was afforded by close agreement of the in vitro d in vivo tryptic peptide maps and by the fact that the bilities of the in vitro products on two-dimensional gels re the same as those of viral proteins labeled in vivo. Gel alysis of in vitro products synthesized from polyoma us-specific RNA in the presence of ^{35}S-formylmethio- -transfer RNA(met)(f) showed that all three proteins were eled. Synthesis of all these proteins was inhibited by 80 M m^7-guanosine triphosphate, suggesting that their RNA's are all capped. The sizes of the major mRNA's for se proteins were determined by gel fractionation to be 4.6 10^5 daltons for VP1, 8.5 x 10^5 daltons for VP2, and 7.4 x 10^5 daltons for VP3. It is concluded that all three proteins e synthesized independently in vitro and are virally coded d that each has a discrete mRNA. (37 refs)

6485 **Splicing of SV40 Late mRNA Is a Post-transcriptional Process.** (Eng) Horowitz, M. (Dept. enetics, Weizmann Inst. Science, Rehovot, Israel); Laub, ; Bratosin, S.; Aloni, Y. *Nature* 275(5680): 558-559; 1978.

licing of simian virus 40 (SV40) late messenger RNA RNA) was investigated by analyzing R-loop structures formed between nuclear (nu) and cytoplasmic (cy) poly(A)+ RNA's and linear SV40 DNA. R loops were obtained by annealing nu or cy 19S poly(A)+ RNA with double-stranded linear SV40 DNA obtained by cleavage of form I DNA with *Bgl*I or *Taq*I restriction endonucleases. The 5′ ends of the nu RNA R loops were closer to the cleavage sites than the 5′ ends of the cy RNA R loops. Free leaders were more common at the 5′ ends of the cy RNA R loops than at the 5′ ends of the nu RNA R loops. The ability of the precursor nu poly-(A)+ viral RNA to anneal to the entire length of the late portion of SV40 DNA (approx 0.67-0.17 map units), including the corresponding interruptions between the leaders and the bodies of the cy mRNA's indicates that splicing is post-transcriptional. Splicing may occur in the nucleus before the RNA molecule is transported to the cytoplasm. However, it is possible that splicing occurs during transport or immediately after transport. The excision-ligation reaction in the precursor molecule is presumably carried out by an enzyme(s) that recognizes short base-paired sequences in this molecule. This reaction would represent a novel mechanism in the regulation of gene expression in animal cells. (17 refs)

78-6486 **Immunocytochemical Evidence for SV40-Related T Antigen in Two Human Brain Tumours of Ependymal Origin.** (Eng) Tabuchi, K. (Dept. Neurological Surgery, Okayama Univ. Medical Sch., 2-5-1 Shikata-Cho, Okayama 700, Japan); Kirsch, W. M.; Van Buskirk, J. J. *Acta Neurochir (Wien)* 43(3/4): 239-249; 1978.

Direct and indirect immunoperoxidase techniques were used to screen 39 human brain tumors for the presence or absence of simian virus 40 (SV40) T antigen. The tumors included 13 glioblastomas, 5 astrocytomas, 1 ependymoma, 1 oligodendroglioma, 1 choroid plexus papilloma, 2 medulloblastomas, 1 neurinoma, 10 meningiomas, 1 hemangioendothelioma, 1 angiofibroma, and 3 metastatic cancers. The nuclei of the ependymoma and the choroid plexus papilloma exhibited a strong positive reaction for T antigen. The remaining 37 tumors were negative for the antigen. In the ependymoma, the presence of T antigen was confirmed by a complement-fixation assay of tumor extract. It is noted that the majority of hamster intracerebral tumors induced by papovaviruses are ependymomas or choroid plexus papillomas. (42 refs)

See also:
*(Rev.): 78-6013, 78-6084, 78-6085, 78-6086, 78-6087, 78-6088, 78-6089, 78-6090, 78-6091, 78-6092, 78-6093, 78-6094, 78-6095, 78-6096, 78-6097, 78-6098.
*(Chem.): 78-6219, 78-6230, 78-6242, 78-6315, 78-6338.
*(Immun.): 78-6489, 78-6496, 78-6497, 78-6499, 78-6500, 78-6501, 78-6503.
*(Path.): 78-6521, 78-6534, 78-6552.
*(Epid.-Biom.): 78-6571.

78-6487 **Evidence of Acquired Immune Deficiencies in Mediterranean Lymphoma. A Possible Aetiological Link.** (Eng) Al-Saleem, T. I. (Dept. Pathology, Coll. Medicine, Univ. Baghdad, Baghdad, Iraq). *Lancet* 2(8092, part I): 709-712; 1978.

Cellular and humoral immunity was systematically studied in 57 patients with α heavy-chain-positive or -negative Mediterranean lymphoma (ML) and 425 controls (healthy volunteers and patients with minor illnesses or other types of lymphoma). Patients with ML had statistically significant reductions in serum IgG and IgM, whereas patients with Hodgkin's disease and nonintestinal non-Hodgkin's lymphoma did not. Impaired cellular immunity was observed in 50% of ML patients challenged with two recall antigens (mumps and purified protein derivative of tuberculin) and with dinitrochlorobenzene. Comparable anergy was found only in patients with advanced Hodgkin's disease. It is hypothesized that repeated exposure of the intestinal epithelium to *Vibrio cholerae* toxin and/or other biologically similar enterotoxins may produce local (and possibly delayed) general impairment of immunity and thus predispose the patient to the development of lymphoplasmacytic neoplasia. Animals that are genetically susceptible to autoimmune disease may be useful as experimental models to test this hypothesis. (35 refs)

78-6488 **Role for Monocyte-Macrophage-derived Colony-stimulating Factor and Prostaglandin E in the Positive and Negative Feedback Control of Myeloid Stem Cell Proliferation.** (Eng) Kurland, J. I. (Dept. Medicine, UCLA Medical Center, Los Angeles, CA); Broxmeyer, H. E.; Pelus, L.M.; Bockman, R. S.; Moore, M. A. *Blood* 52(2): 388-407; 1978.

Female B6D2F$_1$ mouse peritoneal macrophages and human peripheral blood monocytes elaborated colony-stimulating factors (CSF) that stimulated the proliferation in vitro of a class of hematopoietic progenitor cells (colony-forming units-culture, CFU-C) restricted to granulocyte and monocyte-macrophage differentiation. High numbers of monocyte-macrophages had little stimulating activity and were markedly suppressive because of the accumulation of a dialyzable, non-species-specific inhibitor of CFU-C proliferation identified by radioimmunoassay as prostaglandin E (PGE). PGE levels correlated inversely with the incidence of the CFU-C, or committed myeloid stem cells. Indomethacin suppression of PGE synthesis increased the number and size of myeloid colonies stimulated, allowing more accurate estimates of CFU-C incidence. The dose-dependent stimulation of PGE synthesis by macrophages in response to increasing concentrations of CSF was accompanied by progress CFU-C inhibitory activity. When human monocytes we exposed to an extract of human granulocytes that decrea CSF production, monocyte PGE synthesis was reduced nificantly. The findings indicate that the in vitro proliferat of committed myeloid stem cells is regulated by both posit and negative feedback controls involving monocyte-mac phage-derived CSF and PGE, respectively. The balance tween CSF and PGE, factors with mutually opposing actio is determined by an afferent feedback mechanism operat via the intrinsic modulation of macrophage PGE synthe in response to local elevations in CSF concentration. (44 r

78-6489 **Age-dependent Leukemia Produced in Thym tomized AKR Mice by Antiserum to Leuke Cells.** (Eng) Kohn, R. R. (Inst. Pathology, Case Western serve Univ., Cleveland, OH, 44106); Sciotto, C. G.; Hens S. *Exp Gerontol* 13(3/4): 181-187; 1978.

The hypothesis that immunological attack can cause ma nant transformation was tested by treating thymectomiz (Th-x) AKR mice of different ages with rabbit antiser against leukemic cells (ALS), antiserum to nonleukemic c (ANS), and normal rabbit serum (NRS). Groups of you and old non-Th-x mice were also treated with antisera. Th were three series of experiments, one with 366-day-old mi one with 439-day-old mice, and one with seven survivi Th-x controls from the first series treated at 500 days of a Leukemic deaths and ages at death were determined. In first series, by 500 days of age, 9/10 intact mice but only 3/ Th-x mice had died of leukemia, and deaths in the latter w delayed. Three out of five Th-x mice receiving ANS and receiving NRS died from leukemia. All five Th-x mice th received ALS died from leukemia soon after treatment. the second series, among Th-x controls and mice rece ing NRS, only one died from leukemia by 500 days of a On the other hand, 3/7 mice receiving ANS died from l kemia by 500 days of age. In the third series, when ALS w given to 500-day-old Th-x mice, the results were equivoc there were 2 early leukemia deaths, 2 early nonleuken deaths, and 3 survivors. Antisera given to non-Th-x mice c not significantly affect the age at which leukemia develope However, there was no clear leukemia-producing effect antisera in Th-x mice > 500 days old. The leukemoge effect of antiserum in Th-x mice correlated with the antivi (Gross leukemia virus) activity of the serum; the ALS teracted most effectively with the virus and caused the hig est incidence of leukemia. It is concluded that leukemic tra formation is a response to immunological attack on the vir or on cells expressing viral antigens and that an addition age-dependent factor is required for leukemogenesis. (21 re

490 **Macrophages and Resistance to Tumors. II. Influence of Agents Affecting Macrophages and ıyed-Type Hypersensitivity on Resistance to a Tumor ıcing Specific 'Sinecomitant' Immunity: Acquired Resist- as an Expression of Delayed-Type Hypersensitivity.** g) Nelson, M. (Kolling Inst. Medical Res., Royal North re Hosp., Sydney, St. Leonards, New South Wales 2065, tralia); Nelson, D. S. *Cancer Immunol Immunother* 4(2): 107; 1978.

influence of agents affecting macrophages and yed-type hypersensitivity (DTH) on resistance to the ethylcholanthrene-induced fibrosarcoma H-7 (to which ng specific resistance can be induced by a low, non-origenic dose of cells) was determined in CBA/H/WEHI e. The expression of DTH to sheep RBC was inhibited arrageenan (CG: 2 mg/mouse ip), niridazole (200 mg/kg agastrically), reserpine (RP: 1 mg/kg iv), and by le-body irradiation (450 and 550 rads, ^{60}Co source, 37 /min). The specific resistance of immunized mice (2.5 x viable cells sc, 17, 18, or 21 days prior to challenge) to pad challenge with H-7 cells was also inhibited by these nts, as shown by progressive tumor growth in the feet. nor growth in the feet of nonimmunized mice was not cted by radiation or niridazole, but it was inhibited or anced by CG, depending on the dose of tumor cells inject- CG permitted the emergence of tumors from an inoculum 0^4 cells, reduced tumor growth from 5 x 10^4 cells, had effect on growth from 10^5 cells, and increased tumor wth from 5 x 10^5 cells. Also, CG treatment just before llenge with 5 x 10^5 cells led to tumor growth early after llenge, but CG treatment 16-19 days before challenge led ome restriction of growth. Paradoxically, RP inhibited nor growth in nonimmune mice profoundly, which sug- s that some inflammatory reaction may be necessary for survival of tumor cells injected into the footpad. It was suggested that specific, acquired resistance to H-7 is ngly akin to DTH and that mice offer some natural resist- e to this tumor. (36 refs.)

6491 **Tumor Induction in Host-Versus-Graft Disease. I. Clinical and Pathologic Features.** (Eng) Cor- us, E. A. (Dept. Diagnostic Radiology, Yale Univ. Sch. dicine, 333 Cedar St., New Haven, CT, 06510). *Am J Pa-* 90(3): 675-688; 1978.

inatal C57BL/l mice given injections of (SJL/J x /BL/l)F_1 spleen cells developed a runting syndrome desig- ed host-vs-graft disease (HVGD). Mortality from the dis- e was related to the dose of F_1 cells. Acute pathologic nges resembled those occurring in parent-F_1 graft-vs-host ease (GVHD), although plasmacytosis was more pro- nced. Mice who recovered from HVGD showed a slight rease in lymphoma incidence over control mice. Such mice e hyperreactive to the F_1 cells used to initiate the original GD syndrome. Most of the tumors developed in those mals receiving the initial injection of F_1 spleen cells within 24 hr of birth. Tumor incidence was unrelated to the clinical severity of HVGD. By contrast, GVHD in the same strain combination resulted in a much higher incidence of lymphomas in a much shorter time. Parental strain cells were detectable in the F_1 hosts up to the time of tumor development. HVGD has a low tumor induction potential; GVHD has a high tumor induction potential. (29 refs)

78-6492 **Transfer of Viable Putative Preneoplastic Hepatocytes to the Livers of Syngeneic Host Rats.** (Eng) Laishes, B. A. (McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI, 53706); Farber, E. *J Natl Cancer Inst* 61(2): 507-512; 1978.

A new technique for the transfer of freshly isolated, carcinogen-altered hepatocytes containing the marker γ-glutamyl transpeptidase (GT) from male F344 albino rats to syngeneic host rat livers is described. Donor mice were inoculated on day 1 with diethylnitrosamine (200 mg/kg ip), fed 2-acetylaminofluorene (2-AAF: 0.02% of diet) on days 14-28, and given a two-thirds hepatectomy (PH) on day 21; cells were isolated on day 31. Hepatocyte suspensions were prepared by proteolytic enzyme perfusion, and transfer was effected by infusion of 0.3 ml of suspension into the hepatic portal vein of rats that had been fed a control diet or the 2-AAF diet for 7 days. All recipients underwent PH on day 7 or 10. Selective proliferation of GT-positive hepatocytes was induced in the livers of hosts that had been fed 2-AAF: large, macroscopic colonies of altered hepatocytes were generated within 10 days of cell transfer. Quantitation of the number of colonies revealed that prior treatment of hosts with a low dose of 2-AAF was essential or the appearance of large numbers of foci. In addition, the appearance of foci on day 10 depended on the presence of intact, GT-positive hepatocytes in the transferred cell suspensions. (24 refs)

78-6493 **Tumor-associated Transplantation Antigen Distinct from H-2k-like Antigens on a BALB/c (*H-2d*) Fibrosarcoma.** (Eng) Parmiani, G. (Div. Experimental Oncology A, Istituto Nazionale per lo Studio e la Cura dei Tumori, Via G. Venezian 1, 20133 Milan, Italy); Meschini, A.; Invernizzi, G.; Carbone, G. *J Natl Cancer Inst* 61(5): 1229-1234; 1978.

To determine whether the foreign H-2.1, H-2.5, H-2.11, H-2.23, and H-2.25 antigens on the 3-methylcholanthrene (3-MC)-induced (*H-2d*) fibrosarcoma C-1 of BALB/cLacDp (C) mice represent the tumor's individual tumor-associated transplantation antigen (TATA), in vivo immunogenicity tests were performed in C mice (*H-2d*) and in a variety of hybrids of various haplotypes. The C-1 tumor lost its immunogenicity completely in CC3F_1 mice (*H-2d* x *H-2k*) and partially in CAF_1 mice (*H-2d* x *H-2a*). Mutiple immunizations with C-1 cells in C and hybrid mice showed that C mice had in vivo resistance to tumor challenges of 10^5 C-1 cells

(anti-TATA immunity) and production of antibodies to H-2k antigens, as revealed by a complement-dependent cytotoxicity assay of normal C3Hf/HeDp (C3) lymphocytes. No effector lymphocytes to H-2k antigens were found in mice that had detectable levels of anti-H-2k antibodies. $CC3F_1$ animals were unable to mount both anti-TATA and anti-H-2k immune responses, whereas $CAKF_1$, $CBRF_1$ (both *H-2d* x *H-2k*), and, to a lesser extent, CAF_1 mice displayed anti-TATA immunity in the absence of anti-H-2k antibody production. $CD2F_1$ (*H-2d* x *H-2d*) mice behaved like C mice, whereas $CB6F_1$ (*H-2d* x *H-2b*) and $CNIHF_1$ (*H-2d* x *H-2q*) crosses were resistant to tumor challenge but had lower titers of anti-H-2k antibodies than C mice. Anti-H-2k antibody production in C mice peaked after the sixth immunization, with a very low level being evident after one or two immunizations, when a clear antitumor immunity was present. It is concluded that H-2k antigens and TATA are probably independent antigenic entities on C-1 cells. (13 refs)

78-6494 **Stimulating Capacity of Blast Cells from Patients with Chronic Myelocytic Leukaemia, in Blastic Crisis in 'One-Way' Mixed Lymphocyte Reaction: Lack of Evidence for T Lymphoblastic Conversion.** (Eng) Han, T. (Depts. Medicine B and Immunology Res., Roswell Park Memorial Inst., New York State Dept. Health, Buffalo, NY, 14263); Gomez, G. A.; Minowada, J. *Immunology* 35(2): 299-305; 1978.

The stimulatory capacity of fresh leukemia blast cells from patients with Philadelphia chromosome (Ph^1)-positive chronic myelocytic leukemia-blastic crisis (CML-BC, 6 patients), acute myeloblastic leukemia (AML, 10), and T- and null-cell type acute lymphoblastic leukemia (ALL, 1 and 5, respectively) on allogeneic lymphocytes in one-way mixed lymphocyte reactions was studied. The blast cells from the CML-BC patients significantly stimulated the allogenic T lymphocytes. The degree of stimulation increased with the number of blast cells, and there was no apparent difference in stimulatory capacity between myeloid-type and lymphoid-type blasts. The blast cells from the AML patients and from three with null-cell ALL also stimulated allogeneic lymphocytes, but cells from the patient with T-cell ALL and cultured leukemic T lymphoblastoid cells (2 lines) showed no stimulating capacity. The cells from two patients with null-cell ALL were not stimulatory. However, cultured leukemic null cells (4 lines) consistently exerted a strong stimulation in the mixed lymphocyte reaction. The data suggest that leukemic cells from patients with lymphoblastic type CML-BC are not T lymphoblasts, although the possibility that they are non-T/non-B lymphoblasts cannot be ruled out entirely. (22 refs)

78-6495 **Cell-mediated Lympholysis: A Receptor-associated Lytic Mechanism.** (Eng) Gensheimer, G. G. (Transplantation Biology Section, Immunology Branch, NCI, NIH, Bethesda, MD, 20014); Neefe, J. R. *Immunol* 36(1): 54-64; 1978.

The mechanism of cell-mediated lympholysis was invest ed. Two major hypotheses have been proposed to explai relationship between the binding stage and the killing s (1) lysis is a nonspecific result of the intimacy created tween killer and target by specific antigen-receptor bin and (2) lysis is effected by the killer cell receptor itself o a closely linked cell-surface component. Two populatio cytotoxic effector cells were coincubated, one relevantly sitized to the second and the second irrelevantly sensit to a third party; in some cases the third-party cells were added. Relevantly sensitized killers were not lysed when c cubated with either cytotoxic targets alone or with cyto targets and their appropriate third-party targets. It se clear, therefore, that the lytic event in cell-mediated ki is not simply a result of the intimacy created by attacker- get binding. In addition, receptor accommodation does produce an activated state in which killer cells secrete n specific soluble toxic factors. These findings suggest, rat that the lytic event in cell-mediated lympholysis is acc plished by the receptor itself or by a geographically clo linked cell-surface component. (17 refs)

78-6496 **Characterization of T Antigens in Polyoma fected and Transformed Cells.** (Eng) Hutc son, M. A. (Tumor Virology Lab., Salk Inst., PO Box 1 San Diego, CA, 92112); Hunter, T.; Eckhart, W. *Cell* 15 65-77; 1978.

The immunoreactive proteins [tumor (T) antigens] in po ma(Py)-infected 3T6 cells were characterized. The v codes for three species having apparent mol wts of 90, daltons (90K), 60K, and 22K, as determined by polyacr mide gel electrophoresis. The 90K and 22K species produ by a large- and a small-plaque wild-type Py virus have sim mobilities, but the 60K species produced by the small-pla wild-type virus has a higher mobility than the 60K spe produced by the large-plaque form. The relationship of virus-coded 90K, 60K, and 22K T antigens to each othe of interest in view of the existence of at least two differ genetically defined early viral functions. These functions defined by two classes of mutants, the temperature-sensit tsA mutants and the host-range nontransforming hr-t m tants. The 90K species is affected by the tsA mutations, si this species is unstable at the nonpermissive temperature cells infected by seven tsA mutants. The 60K and 22K spec are stable under the same conditions. Only the 22K spec is present in cells infected by a mutant carrying a deleti between roughly 98 and 3 map units in the early region the viral genome. Tryptic peptide analysis of the isolat 90K, 60K, and 22K species shows that the three have fo peptides in common. These peptides may be derived from common N terminal region. The 60K and 22K species co tain amino acid sequences not found in the 90K species, a the 60K species has several unique methionone-containi

ides not found in the 22K or 90K species. The observa- that two BHK cell lines transformed by Py virus do not ain detectable amounts of the 90K T antigen is consistent previous observations that permissive or semipermissive oma-transformed cells fail to contain stable cytoplasmic A corresponding to the distal portion of the early region ie Py genome. The tsA function may be involved in regu- g the growth properties of some transformed cells, be- e some cells transformed by a Py tsA mutant show tem- ture-dependent growth properties. (27 refs)

6497 Specificity and Age of Appearance of Natural Immunity to MTV Antigens. (Eng) Lopez, D. (Lab. Virology, Dept. Microbiology, Univ. Miami, Sch. licine, Miami, FL, 33152); Sigel, M. M.; Ortiz-Muniz, G.; cs, W. *Proc Soc Exp Biol Med* 158(1): 23-27; 1978.

natural immune reactivity of BALB/c mice to mammary or virus (MTV) antigens was examined by lymphocyte sformation and migration inhibition assays. The specifici- f the lymphocyte response to RIII MTV was measured virus neutralization reactions using anti-MTV and an- auscher leukemia virus (abtu-RLV) sera. The former in- ted the blastogenic response to MTV, but the latter had effect. RLV did not induce transformation in BALB/c phocytes. MTV-induced lymphocyte transformation was erved at low levels and in a small percentage of LB/cCrgl mice as early as 2 wk after birth. At 8 wk of the responses in the lymphocyte transformation and mi- ion inhibition assays were intermediate in frequency /or intensity, and by 16 wk, essentially max responses e seen. The nature of the antigen responsible for the lym- cyte sensitivity has not been determined, but radioim- noassays have largely ruled out the MTV p14 antigen. It ypothesized that lymphocyte sensitivity to MTV antigen inates from the occurrence of a viral antigen produced the expression of part of the viral genome in the host omosome. (23 refs)

6498 Leukaemia Associated Antigens: Expression by Human Cell Lines. (Eng) Bertoglio, J. (Labora- e d'Immunologie et de Cancerologie Experimentale, tre Leon Berard, 28 rue Laennec, 69373 Lyon Cedex 2, nce); Dore, J. F. *In: Human Lymphocyte Differentiation: Application to Cancer. Proceedings of the International mposium on Human Lymphocyte Differentiation: Its Ap- ation to Cancer, held in Montpellier (France) by Institut tional de la Sante et de la Recherche Medicale and Delega- Generale a la Recherche Scientifique et Technique, 2-4 rch, 1978.* Serrou, B., Rosenfeld, C., eds. (Amsterdam: rth Holland Publishing Company): 423 pp.; 357-364; 8.

rteen human lymphoid cell lines derived from normal B phocytes or from patients with leukemia, lymphoma, or Burkitt's lymphoma were tested for expression of leukemia-associated antigens using sera from leukemia patients and normal donors cytotoxic to human leukemia cells and relatively specific for acute lymphoblastic leukemia (ALL). None of the lines derived from the normal B lymphocytes or from patients with Burkitt's lymphoma were reactive. Only four lines, derived from patients with ALL, acute myelomonocytic leukemia, the blastic crisis of chronic myeloid leukemia, and lymphosarcoma, respectively, were reactive with one or more of the 10 sera used. The Reh line, derived from a patient with non-T, non-B ALL, was the most reactive and the only one to react with patients' sera. Cells from a fifth line (derived from a patient with ALL) were able to absorb the reactivity of one serum (MOR: from the father of a leukemia patient) to ALL cells, as were all three cell lines that were reactive with serum MOR in the direct test. Thus, permanent cell lines of leukemic origin may be useful in the study of leukemia-associated antigens. (19 refs)

78-6499 Humoral and Cellular Immune Response of Prostatic Cancer Patients to Cytomegalovirus-related Antigens. (Eng) Sanford, E. J. (Div. Urology, Milton S. Hershey Medical Center, Pennsylvania State Univ., Hershey, PA, 17033); Geder, L.; Dagen, J. E.; Laychock, A.; Rohner, T. J.; Rapp, F. *J Surg Res* 24(5): 404-408; 1978.

The association between prostatic adenocarcinoma and cytomegalovirus (CMV) infection was investigated in patients with biopsy proved adenocarcinoma or benign prostatic hypertrophy (BPH). Humoral immune response studies were performed to detect antibodies against human embryonic lung cells (HEL), HEL transformed by CMV (CMV-Mj-HEL-2), and cells from a CMV-Mj-HEL-2-induced tumor in nude mice (CMV-Mj-HEL-2, T-1). Neither the cancer nor BPH patients had antibodies against HEL or CMV-Mj-HEL-2 cells, but 80% of the cancer patients and 68% of the BPH patients had antibodies against CMV-Mj-HEL-2, T-1. In cellular immune response studies, 82% of the cancer and 35% of the BPH patients had lymphocytes cytotoxic to CMV-Mj-HEL-2 cells, 82% and 90%, respectively, had lymphocytes cytotoxic to CMV-Mj-HEL-2, T-1 cells, and 20% of both groups had significant cytotoxicity to HEL cells. Sera from prostatic carcinoma patients significantly blocked the cytotoxicity of lymphocytes from prostatic cancer patients against CMV-Mj-HEL-2, T-1 to a greater degree than it did lymphocytes from nontumor controls. Sera from the nontumor controls exhibited little blocking activity. Hyperimmune rabbit anti-CMV sera did not block the cytotoxicity of cancer patient sera and, in fact, enhanced the cytotoxic effect in 2/3 patients. The results suggest that prostatic carcinoma patients possess a serum blocking factor that may be a CMV-related antigen-antibody complex. (18 refs)

78-6500 Specific Immune Response Against Tumor-associated Antigens of a Syngeneic Simian Virus

40-induced Sarcoma in Mice. (Eng) Glaser, M. (Lab. Cell Biology, Immunology Program, Div. Cancer Biology and Diagnosis, NCI, NIH, Bethesda, MD, 20014). *J Natl Cancer Inst* 61(5): 1351-1355; 1978.

An immune response against syngeneic simian virus 40 (SV40)-induced tumor-associated antigens (TAA) in (BALB/c x C57Bl/6)F_1 female mice was detected by in vivo tumor challenge and tumor cell neutralization tests and by the in vitro ^{51}Cr-release cytotoxicity assay. All mice immunized with 1 x 10^5 SV40-transformed cells were protected against the growth of SV40-induced tumor from 3 to 90 days after a single immunization. In the tumor cell neutralization test, spleen cells (T cells) from mice immunized with 1 x 10^6 transformed cells prevented tumor growth from 10 to 90 days after immunization. Spleen cells from mice immunized with a minimum of 20 x 10^6 transformed cells were cytotoxic in vitro against the relevant target cells in a 4-hr ^{51}Cr-release cytotoxicity assay. Cytotoxic lymphocytes were detected 3 days after immunization, reached a peak activity at 8 days, and declined to low levels at 14 days. At all times after immunization, T cells were needed for cytotoxic reactivity to be eliminated by specific anti-θ serum and complement. (21 refs)

78-6501 **Stimulatory Effect of Immunization on Tumor Induction by Moloney Murine Sarcoma Virus.** (Eng) Murasko, D. M. (Dept. Microbiology, Medical Coll. Pennsylvania and Hosp., 3300 Henry Ave., Philadelphia, PA, 19129); Prehn, R. T. *J Natl Cancer Inst* 61(5): 1323-1327; 1978.

Adult BALB/c mice were immunized with varying doses of inactivated Moloney murine leukemia virus (M-MuLV) and challenged 8 wk later with 0.1 ml Moloney murine sarcoma virus (M-MuSV), at a dose that induces tumors in 50% of normal animals. Sera from all immunized mice demonstrated neutralizing activity 14 days after immunization in the XC assay. The ability of sera to neutralize M-MuLV was directly related to the amount of M-MuLV used for immunization. No neutralizing activity was detected in any serum sample taken 8 wk after immunization. Mice immunized with high doses (10^{10} particles) of M-MuLV had significantly decreased tumor incidences, whereas mice immunized with low doses (10^2 particles) had significantly increased tumor incidences, compared with those in nonimmunized controls. The stimulatory effect could be abrogated by irradiation of the mice with 450 rads 24 hr prior to M-MuSV challenge, but the inhibitory effect was resistant to this treatment. The results suggest that depending on dose, immunization with virus can either stimulate or inhibit virus-induced tumorigenesis. Two possible explanations for the mechanism of increased tumorigenesis are suggested: (1) direct stimulation of target cells by lymphoid cells or lymphoid cell products; and (2) suppression of an inhibitory immune response. (33 refs)

78-6502 **Resurgence of Killing and In Vivo Protection Mediated by Lymphocytes Cultured from Lymph Nodes Draining Moloney Sarcomas.** (Eng) Gilles G. Y. (Dept. Pathology, Univ. North Carolina Sch. M cine, Chapel Hill, NC, 27514); Hansen, C. B.; Russell, S. *Br J Cancer* 38(3): 365-374; 1978.

The return of cytolytic activity to tumor-draining lyn node cells that were no longer cytotoxic in vivo was inve gated. The popliteal and lumbar lymph nodes draining gressing or progressing Moloney sarcomas in male BAL AnCr mice were removed from the animals and minced, the lymphocytes were isolated. The lymph node cells were no longer cytotoxic in vivo spontaneously regenera peak levels of killing after a 4-day in vitro culture in absence of exogenous tumor antigen. Cytolytic activ which was antigenically specific, was mediated by T c Resurgence of cytolytic activity in vitro was accompanied proliferative changes (DNA synthesis, blast transformati cell division) that peaked on day 3 of culture. Although n mal, nonimmune lymph node cells underwent quantitativ similar proliferative changes in culture, the killing that de loped was weak and antigenically nonspecific. Transfer cultured, tumor-draining lymph node cells to immunologi ly compromised, syngeneic mice conferred complete prot tion from Moloney sarcoma progression. Adoptive trans could be delayed for 6 days after tumor induction with loss of protection. These findings suggest that some me anism in Moloney sarcoma-bearing mice limits the differ tiation of prekiller cells into cytolytically active T cells a that this inhibition is eliminated when the lymph node c are explanted into culture. (31 refs.)

78-6503 **Activation of Complement by Spontaneous L kemic Cells of AKR Mice.** (Eng) Okada, (Dept. Bacteriology, Kitasato Inst., Shirogane 5-9 Minato-ku, Tokyo 108, Japan); Okada, H. *Int J Cancer* 22(282-287; 1978.

The extent of nonspecific activation of complement (NA by AKR mouse spontaneous leukemic and normal cells w compared by the human erythrocyte (E) rosette formati following treatment of cells with C4-deficient guinea serum in the presence of Mg^{2+}/gelatin veronal-buffer saline/ethyleneglycolbis(β-aminoethyl ether) N,N'-tetraa tate (EGTA) and in the absence of Ca^{2+}. Following tre ment, 10%-30% of lymphoma cells and 10%-17% of thym ma cells formed rosettes, vs only 3%-4% of thymus a mesenteric lymph node cells from nonleukemic mice. T percentage of NAC-positive cells was essentially the same the original spontaneous, transplanted (to nonleuken mice), and cultured lymphoma cells, indicating that NA ability does not result from antigen-antibody-compleme complexes that are formed or fixed in vivo. The results su gest that NAC ability may be increased when normal AK cells become transformed into leukemic cells and/or that t leukemic cells arise from thymus cells that possess NAC ab ity. This interpretation was confirmed further by the findi that a higher proportion of leukemic cells than that of norm

nocytes were lysed by mouse complement in Mg^{2+}-
'A. The fact that NAC-positive AKR thymoma cells
lysed more effectively by homologous C3H/He mouse
ma than by the guinea pig serum agrees with earlier find-
that a temporary regression of leukemia occurs in leu-
ic AKR mice supplemented with C5. (30 refs)

6504 Characterization of Fc Receptor in Human Malignant Tumors (Meeting Abstract). (Eng) hnan, E. C. (Coll. Health Science and Hosp., Univ. Kan- Medical Center, Kansas City, KS, 66103); Jewell, W. R. *Am Assoc Cancer Res* 19: 96; 1978. (no refs)

5505 Cell Receptor Studies on Six Anaplastic Tumours of the Thyroid. (Eng) Macaulay, R. A. pt. Forensic Medicine, Univ. Edinburgh, Edinburgh, tland); Dewar, A. E.; Langlands, A. O.; Stuart, A. E. *J n Pathol* 31(5): 461-468; 1978.

attempt was made to distinguish malignant lymphoma n other thyroid tumors by examining suspensions of tu- r cells for lymphocyte surface markers. The results were related with the ultrastructural appearance of the tumors, clinical extent of the disease, and response to radiothera- Cell suspensions were obtained from the anaplastic thy- d tumors of six patients (5 women, 1 man, aged 60-85). gave a history of rapid enlargement of the thyroid gland. five cases, many of the cells showed surface immunoglobulin. Electron microscopy studies of three of these tumors were indicative of malignant lymphoma. In 2/5 cases, the patients had a history of previous thyroid disease. The single tumor that did not show surface immunoglobulin had an entirely different ultrastructure and was probably a carcinoma. This patient was the only one that did not achieve complete remission with radiotherapy, and she died from extensive local recurrence. It is concluded that receptor techniques are of value in distinguishing between malignant lymphoma and other anaplastic tumors of the thyroid, particularly when the results are correlated with histology. (23 refs)

See also:
*(Rev.): 78-6013, 78-6071, 78-6072, 78-6076, 78-6077, 78-6078, 78-6079, 78-6080, 78-6081, 78-6082, 78-6083, 78-6088, 78-6098.
*(Chem.): 78-6209, 78-6219, 78-6277, 78-6278, 78-6310, 78-6332.
*(Viral): 78-6400, 78-6402, 78-6406, 78-6427, 78-6430, 78-6432, 78-6435, 78-6442, 78-6443, 78-6444, 78-6446, 78-6449, 78-6452, 78-6459, 78-6460, 78-6468, 78-6473, 78-6479.
*(Path.): 78-6514.

78-6506 **Genetically Determined Sex-Reversal in 46,XY Humans.** (Eng) German, J. (New York Blood Center, 310 E. 67 St., New York, NY, 10021); Simpson, J. L.; Chaganti, R. S.; Summitt, R. L.; Reid, L. B.; Merkatz, I. R. *Science* 202(4363): 53-56; 1978.

Observations of one family that constitute strong evidence for the existence in humans of an X-borne gene that in mutant form results in sex-reversal in 46,XY individuals are reported. They also provide further insight into the genetic control of normal human gonadal differentiation. Affected were two sisters, their maternal aunt, and one first cousin from another maternal aunt. All four developed normally throughout childhood. At puberty, axillary and pubic hair developed normally, but breast development and menstruation had to be induced by appropriate hormones. None of the four displayed Turner's syndrome characteristics. Genitalia were unambiguously female, and uterus and fallopian tubes were normal at prepubertal age. Upon pelvic surgery (between age 19 and 29), however, the sisters were found to have bilateral streak gonads reminiscent of 45X gonadal dysgenesis. The cousins's gonads were grossly streaklike, but were proved to be bilateral gonadoblastomas. Pathology of an abdominal tumor removed from the aunt is unknown, but suspect. Chromosome studies of the three living women (the aunt died postoperatively) ruled strongly against mosaicism. X and Y chromosomes appeared normal in banding studies. The inability of the Y chromosome alone to initiate male differentiation of the embryo was ruled out, because three of the Y chromosomes came from different fathers. Therefore, it was hypothesized that some X-Y interaction is necessary for the initiation of male differentiation and that in these women the necessary X locus was mutant, perhaps transmitted as an X-linked recessive trait. In the absence of male differentiation and in the presence of only one X, the sexual differentiation resulting in streak gonads was like that seen in 45X gonadal dysgenesis. (27 refs)

78-6507 **Uneven Geographical Distribution of 15;17-Translocation in Acute Promyelocytic Leukaemia (Letter to Editor).** (Eng) Teerenhovi, L. (Third Dept. Medicine, Univ. Helsinki, SF-00290 Helsinki 29, Finland); Borgstrom, G. H.; Mitelman, F.; Brandt, L.; Vuopio, P.; Timonen, T.; Almqvist, A.; de la Chapelle, A. *Lancet* 2(8093): 797; 1978.

In contrast to findings in Belgian and, perhaps, US patients, none of the nine Finnish and three Swedish patients with acute promyelocytic leukemia (APL) examined (comprising all cytogenetically analyzed cases from Finland and southern Sweden) had a 15;17-translocation. Apparently, there is a striking difference in the geographical distribution of t chromosome anomaly in APL patients. (10 refs)

78-6508 **Simultaneous Occurrence of Non-Hodgki Lymphoma and Spontaneous Acute Granuloc ic Leukemia.** (Eng) Youness, E. (Dept. Lab. Medicine, D. Anderson Hosp. and Tumor Inst., 6723 Bertner Av Houston, TX, 77030); Ahearn, M. J.; Drewinko, B. *Am Clin Pathol* 70(3): 415-420; 1978.

The second reported case of simultaneous non-Hodgki lymphoma and spontaneous acute granulocytic leukemia o curred in a 67-yr-old Caucasian farmer. He had no remark ble family or medical history except for chronic exposure some form of insecticide. The diagnoses of the two diseas were confirmed by examination of the patient's bone marro and peripheral blood specimens at the light and electron m croscopic level and by autopsy findings. Comparison of th patient with the previously reported patient (a woma showed that both had no prior history of chemotherapy an or radiotherapy, they were in their late 60's, they had rel tively short histories of anemia and wt loss, and they ha simultaneous involvement of lymphopoietic organs and pe pheral blood. The woman had generalized lymphadenopath and blast-containing Auer rods, but the man had lympho involvement confined to the liver, spleen, and bone marro and his blasts did not show Auer rods. Chronic exposure t an unknown insecticide may have played a leukemogenic ro in the latter. (32 refs)

78-6509 **Probable Clonal Origin of Acute Myeloblasti Leukemia Following Radiation and Chemoth erapy of Colon Cancer.** (Eng) Wiggans, R. G. (Dept. Medi cine, Div. Medical Oncology, Georgetown Univ. Hosp., Vin cent T. Lombardi Cancer Res. Center, Georgetown Univ Washington, DC); Jacobson, R. J.; Fialkow, P. J.; Woolley P. V.; Macdonald, J. S.; Schein, P. S. *Blood* 52(4): 659-663 1978.

Acute myeloblastic leukemia (AML) developed in a 64-yr-old black woman after radiation and drug therapy for disseminat ed colon cancer. The occurrence and then progression of pul monary metastases prompted two ^{60}Co-radiation treatment (3,500 and 4,200 rads) 3 and 1 yr before AML diagnosis respectively. She was also treated with cytotoxic drugs in the 2 yr prior to diagnosis, including intermittent courses o 5-fluorouracil throughout that time and, in the year preced ing diagnosis, with 1-(2-chloroethyl)-3-(4-methylcyclohex yl)-1-nitrosourea (4 mo) and streptozotocin (3 wk). Approx

l amounts of B and A types of glucose-5-phosphate dehyenase were found in skin and cultured skin fibroblasts, only type B was detected in the abnormal WBC. In mosome studies, cultured cells from normal tissues were X, but all 90 unstimulated blood cells studied were missapprox two-thirds of the short arms of chromosome 12 XX,12p-). This abnormality was also detected in 18/24 imulated marrow cells. These data are consistent with a al origin of this leukemia. (23 refs)

510 **Multifocal Histogenesis of a Cystosarcoma Phyllodes.** (Eng.) Salm, R. (Dept. Histopathol-Royal Postgraduate Medical Sch., Hammersmith Hosp., ane Road, London W12 0HS, England). *J Clin Pathol*): 897-903; 1978.

unusual multifocal cystosarcoma phyllodes (CSP) oced in a 50-yr-old woman. The CSP presented as a small, umscribed tumor mass, and it was associated with two se neoplastic lesions that arose sequentially in two sepa- parts of the mammary disk. Microscopically, the tumor ared to have been enlarging by the formation of isolated llite tumor nodules within the adjacent normal breast tis- This represents a third mechanism by which CSP may rge, the other and more common modes being expansion within and extension of tumor projections from the pery. (6 refs)

511 **Soft Tissue Sarcomas in the Cat.** (Eng) Brown, N. O. (Donaldson-Atwood Cancer Clinic, Ani- Medical Center, 510 E. 62nd St., New York, NY, 10021); aik, A. K.; Mooney, S.; Hayes, A.; Harvey, H. J.; Ewen, E. G. *J Am Vet Med Assoc* 173(6): 744-749; 1978.

trospective survey was made of the soft tissue sarcomas id in 23 cats at an animal medical center from 1971 to . The nature of the tumors was variable. All tumors tend- develop in older cats and in various locations, although were on the extremities. Diagnosis was made upon biop- No feline leukemia virus was detected in the 13 cats tested. refs)

512 **Connection Between Accidental Trauma and Course of Malignant Melanoma of the Skin.** r) Wozniak, K. D. (Universitats-Hautklinik, Ernst- mayer-Strasse 5/8, DDR-402 Halle [S], E. Ger- y). *Dermatosen Beruf Umwelt* 26(5): 166-168; 1978.

se of malignant melanoma that may have been acceleratnto rapid metastasis by trauma is described. A 38-yr-old who had a lentil-sized nevus above his left knee for as as he could remember presented with painful ph-node swelling in the left groin. He reported that the nevus had been growing for 6 mo. At presentation it was cherry-sized, half-spherical, gray-black, tender, and eroded. After this tumor was removed it was identified as a melanocytoblastoma, partly round-cell and partly spindle cell in composition. The inguinal lymph nodes were also removed. They had the same histology as the tumor. The patient was wounded in the area of the nevus 4 mo before presentation; the wound caused erosion of the nevus. An inflammatory reaction resulted and lymphangitis followed soon after. The patient was symptom-free for 3 mo after treatment, but then neurological symptoms appeared. In spite of intensive therapy, the patient died of heart failure. At autopsy, generalized metastases of the melanoma were found in the iliac artery and aorta, liver, and spleen. Although trauma is no longer considered a cause of melanoma, trauma to a nevus that has begun to undergo malignant transformation may accelerate the course of the disease, as suggested by this case. (24 refs)

78-6513 **Malignant Lymphoproliferative Disorders in Chronic Liver Disease. Report of Four Cases and Review of the Literature.** (Eng) Naparstek, J. (Dept. Medicine, Hadassah Univ. Hosp., Jerusalem, Israel); Eliakim, M. *Am J Dig Dis* 23(10): 887-892; 1978.

The case reports of four patients (3 men, 1 women 54-61 yr old) with chronic liver disease who later developed lymphoma are given, and the related literature is reviewed. Three of the patients had nonalcoholic cirrhosis and one had chronic cholangitis. Non-Hodgkin's lymphoma developed long after the presence of liver disease had been established in three patients; the fourth died of hepatic coma, and Hodgkin's disease was discovered incidentally at autopsy. No drugs could be implicated in the appearance of the liver disease or the lymphoma. The findings of these four cases within a relatively short period suggests that the association between the two conditions is not incidental. A review of the literature yielded 40 additional cases. In many, lymphoma complicated long chronic liver disease; in others, however, liver disease was secondary to hepatitis B infection or to treatment of lymphoma. Among the several mechanisms that may be operative in the pathogenesis of lymphoma in patients with liver cirrhosis, chronic antigenic stimulation, the presence of hepatitis B surface antigen, and immunosuppressive therapy seem to be the most important. (44 refs)

78-6514 **An Unusual Case of Bence-Jones Myeloma with Unreleased γ Heavy Chains in the Cytoplasm of the Myeloma Cells: A Close Relationship Between Bence-Jones Myeloma and Nonsecretory Myeloma.** (Jpn) Kanoh, T. (First Div., Dept Internal Medicine, Faculty Medicine, Kyoto Univ., Kyoto, Japan); Dohmae, N.; Uchino, H.; Sugimoto, C.; Shimada, T. *Acta Haematol Jpn* 41(5): 938-944; 1978.

A case of Bence Jones (K) partially nonsecretory myeloma with unreleased γ heavy chains in the cytoplasm of the myeloma cells is presented, and the close relationship between Bence Jones myeloma and nonsecretory myeloma is discussed. Bence Jones myeloma arises from one of the following mechanisms, most of which are common to nonsecretory myeloma: (1) loss of the capacity to synthesize heavy chains (Bence Jones myeloma without heavy-chain synthesis); (2) loss of the capacity to secrete whole molecules of immunoglobulins, with secretion of light chains only (Bence Jones myeloma with heavy-chain synthesis); and (3) secretion of immunoglobulins with an abnormal heavy or light chain and their rapid extracellular degradation (Bence Jones myeloma without detectable immunoglobulin synthesis). The pathogenesis of the present case may be due to mechanism 2. The characteristic picture of myeloma cells filled with numerous Russell bodies in the present case might be related to the presence of unreleased γ heavy chains in the cytoplasm. (19 refs)

78-6515 **Radium-Induced Cancer: Excessive Radium Dosage (Meeting Abstract).** (Eng) Applebaum, E. L. (Glencoe, IL). *Otolaryngology* 86(4): 188-189; 1978. (no refs)

78-6516 **Tumor and Tumor-like Lesions of Perilimbal Conjunctiva in Laboratory Dogs.** (Eng) Hargis, A. M. (Collaborative Radiological Health Lab., Dept. Pathology, Colorado State Univ., Fort Collins, CO, 80523); Lee, A. C.; Thomassen, R. W. *J Am Vet Med Assoc* 173(9): 1185-1190; 1978.

Among 1,680 research colony beagles, proliferative and neoplastic lesions developed in the nasal or temporal limbal conjunctiva of 8 male and 6 female dogs. The mean age at observation was 5.2 yr. Acanthosis and squamous cell carcinoma of the conjunctival epithelium to vascular ectasia, hemangioma, and invasive hemangiosarcoma of the underlying lamina propria were seen. The dogs had been kept in a sunny, relatively high-altitude (1,500 m), smog-free area, suggesting that exposure to solar radiation may have been involved in tumor development. (19 refs)

78-6517 **Cerebellar Medulloblastoma: An Analysis of Four Cases of Extraneural Metastasis.** (Eng) Schnitzler, E. R. (Dept. Neurology, Univ. Wisconsin, 1300 University Ave., Madison, WI, 53706); Richards, M. J.; Chun, R. W. *Am J Dis Child* 132(10): 1004-1008; 1978.

The cases of 4/28 medulloblastoma patients who developed extraneural metastases are reviewed, and their clinical features are compared with those of the 24 patients without metastases. Suboccipital craniectomy, radiation therapy, and patient longevity were not well-correlated with metas
However, subarachnoid tumor spread was a consistent
cursor (4/4 patients with metastasis vs 7/24 without). A
triculoatrial shunt may have been a factor in one patient,
a serious infection that preceded diffuse metastases may
been a factor in another. Two of the four patients with m
tases had the desmoplastic variety of medulloblastoma,
only 1/24 without metastases had this variant. Identifica
of the medulloblastoma patient with an increased risk o
traneural metastasis is difficult but it has practical imp
tions, since recent studies indicate that this metastasis is
sitive to chemotherapy. (21 refs)

78-6518 **Linkage Study in a Kindred with Multiple docrine Neoplasia (MEN 11) (Meeting stract).** (Eng) Forster, C. J. (Queen's Univ., Toronto, tario, Canada); Sears, E.; Ghent, W.; Falk, J.; Goodall Partington, M. W.; Simpson, N. E. *Can J Genet Cytol* 2(443; 1978. (no refs)

78-6519 **Squamous Cell Carcinoma Arising in a Me gomyelocele.** (Eng) Saksun, J. M. (Div. I matology, Dept. Medicine, Wellesley Hosp., 160 Welle St., E., Toronto, Ontario M4Y 1J3, Canada); Fisher, B *Can Med Assoc J* 119(7): 739-741; 1978.

A squamous cell carcinoma arose in a lumbosacral me gomyelocele of a 25-yr-old man. Only two similar cases w found in the literature. Neoplastic change in untrea meningomyeloceles is possible after years of mechanical i tation due to braces and chronic bacterial infection. (28 r

78-6520 **Pathogenesis of Attic Cholesteatomas.** (E Sade, J. (Meir General Hosp., Kfar Saba, Isra *J R Soc Med* 71(10): 716-732; 1978.

To determine the mode of genesis of attic cholesteato (AC), 22 of these tumors were investigated in situ and in to They were all epidermoid cysts of elaborate cellular organi tion, 18 of which were situated medial to the ossicular cha This site makes self-cleansing difficult, producing seconda infection. Three AC had no connection with the external canal. However, whether or not AC communicate with external canal, they have a lining that often has mixed e thelium: stratified squamous epithelium (EC) synthesizi keratin and respiratory epithelium producing mucus. T shows that a metaplastic process is involved, at least to so degree. Therefore, AC are epidermoid cysts that origina primarily in the attic from epithelial cells that metaplastica mature into keratinizing epithelium. They often prese themselves secondarily in the external canal as a perforat epidermoid cyst. The favored etiology of an invasive retra tion from the external ear is difficult to accept in view of t

ıtact inhibition of the SE or the invariable outward migra-
ı of stratified SE from the edges of retraction pockets as
ll as from cholesteatoma perforations. Also, there is no
:umentation of an evolution of AC from preexisting perfo-
ions or from marginal perforations. (47 refs)

-6521 **Intranasal Tumor of the Ethmoid Olfactory Mucosa in Sheep.** (Eng) Yonemichi, H. ıkikawa Animal Husbandry Experimental Station, Hok-
do, Takikawa 073, Japan); Ohgi, T.; Fujimoto, Y.; Okada, ; Onuma, M.; Mikami, T. *Am J Vet Res* 39(10): 1599-1606; 78.

ranasal tumors (papillary adenomas or adenocarcinomas) the ethmoid olfactory mucosa of sheep were investigated light and electron microscopy. The fine structure of the nor cells was characterized by the presence of numerous retory granules. Viral particles that were morphologically nilar to a visna-maedi virus were detected in all tumor tis-es and in 3/4 cultures examined. The particles [93-97 na-meters (nm)] had an eccentrically located electron-dense re (47 nm), often surrounded by a single (intermediate) embrane; these particles also had numerous spikes (9 nm) their surfaces. There were no viral particles in the lung sheep with pneumonia or in the normal olfactory mucosa two control sheep. RNA-dependent DNA polymerase DDP) activities in the tumor tissues or in cultured tumor lls were greater than those in normal intranasal tissues or ltured cells from the choroid plexus. Viral particles similar herpesvirus were also detected in one culture, and particles a paravaccinia type were found in another. (28 refs)

8-6522 **Familial Medullary Thyroid Carcinoma.** (Eng) Hillyard, C. J. (Dept. Surgery, Royal Postgradu-
e Medical Sch., Hammersmith Hosp., Ducane Road, Lon-
on W12 0HS, England); Evans, I. M.; Hill, P. A.; Taylor, *Lancet* 1(8072): 1009-1011; 1978.

wenty-one relatives of a 14-yr-old girl with medullary thy-
oid carcinoma (MCT) were screened by the plasma calcito-
n assay before and after alcohol provocation. The patient's ther and two siblings had raised basal levels, and the diag-
osis of MCT was confirmed at surgery; their calcitonin lev-
s became undetectable after total thyroidectomy. Only 1/3 ad a palpable thyroid mass. Three more distant relatives had etectable calcitonin levels after alcohol stimulation, and ey are being rescreened at regular intervals. Cervical lymph ode metastases were found in the index patient 1 mo after otal thyroidectomy. Her current calcitonin level is now 36.8 g/liter. (9 refs)

3-6523 **Total Thyroidectomy: The Indications and Results of 630 Cases.** (Eng) Katz, A. D. (8733 Beverly Blvd., Los Angeles, CA, 90048); Bronson, D. *Am J Surg* 136(4): 450-454; 1978.

Indications for total thyroidectomy are illustrated in a series of 630 patients (499 females, 131 males aged 7-83 yr) in whom this operation was performed during 1958-1978 in Los Angeles County. The patients were divided into three groups: (I) 121 with Grave's disease; (II) 133 with a history of childhood head, neck, and thorax irradiation and a cold thyroid nodule; and (III) 396 with a dominant cold thyroid nodule suspected of being a carcinoma. The total cancer incidence was 193/630 patients: 183 had papillary follicular carcinoma, 4 medullary carcinoma, 5 anaplastic or small cell carcinoma and 1 reticulum cell sarcoma. Group I patients had a 5% malignancy rate, Group II a 42.5% rate, and Group III a 35% rate. Concerning Group II patients, available data indicate that at least 2% of individuals whose thyroids were exposed to 300 rads of x-rays will develop thyroid cancer within 25 yr and that 9% will have benign nodules. Irradiation of thymolymphatic tissue in the head, neck, and thorax might result in changes in lymphoid elements that subsequently reach the thyroid gland. Lymphoid elements are far more vulnerable to radiation-induced changes than thyroidal epithelium. In most of the 113 Group II patients, both lobes of the thyroid were grossly and microscopically abnormal (follicular and Hurthle cell adenomas, multicentric carcinomas, and thyroiditis). (25 refs)

78-6524 **Synovial Sarcoma of the Neck.** (Ita) Bertoni, F. (Servizio di anatomia ed istologia patologica, Ospedale Marcello Malpighi di Bologna, Bologna, Italy); Bacchini, P. *Pathologica* 70(1005/1006): 409-418; 1978.

The case of a 42-yr-old woman with synovial sarcoma of the neck is reported. The patient had symptoms of pain in the neck region, swelling, and hoarseness. Examination of the larynx revealed a polypous neoplasm on the posterior and lateral walls of the pharynx. A biopsy was performed, and a diagnosis of synovial sarcoma was made. The patient underwent a partial pharyngectomy and a total laryngectomy. No evidence of metastases to the cervical lymph nodes was found. Microscopically, fused cells were seen with voluminous nuclei and a granular-eosinophilic cytoplasm. The nuclei were polydimensional, with indented and jagged membranes. Histologically, the neoplasm was composed of two components: epitheliallike and mesenchymal. The epithelial-like components (PAS- and Alcian-positive) formed pseudoglandular formations. The mesenchymal component was pressed between these formations and was rarely PAS- or Alcian-positive. The histological aspects confirmed the diagnosis. (15 refs)

78-6525 **Mammary Gland Hyperplastic Alveolar Noduligenesis in the LEW/Mai Rat in Relation to Mitotic Activity. Estrous Cycle Status, and Age.** (Eng)

Purnell, D. M. (Dept. Pathology, Sch. Medicine, Univ. Maryland, 660 W. Redwood St., Baltimore, MD, 21201); Stowers, D. J. *J Natl Cancer Inst* 61(5): 1339-1346; 1978.

The genesis of spontaneous mammary hyperplastic alveolar nodules (HAN) was studied in nulliparous female LEW/Mai rats in relation to age, estrous cycle status, and mammary gland mitotic activity. Mitotic activity in the contralateral mammary gland rose almost linearly from 30 to 108 days of age and then fell progressively, although it remained significantly higher than the activity in mammary glands of rats < 100 days old. Mitotic activity was nonrandomly distributed in the mammary glands of young pubertal rats in contrast to that in glands of prepubertal rats and in rats in persistent estrus. The percentage of rats with HAN as well as the incidence of HAN in the inguinal mammary gland increased progressively with age. At 150 days of age, 12.5% of the rats had 1-5 HAN/inguinal mammary gland; by 183 days, 18.5% had 1-19 HAN/gland; and by 215 days, 91.7% had 3-44 HAN/gland. HAN were more common near the nipple than in other regions of the mammary gland. They appeared only in rats in persistent vaginal estrus, and they were more frequent in rats that displayed this condition for the longest period of time. Rats with HAN also had significantly increased pituitary wts. These findings suggest that hormone imbalance may be an important etiologic factor in the genesis of spontaneous HAN in rats. (20 refs)

78-6526 **Phagocytosis of Tumor Cells by Murine Kupffer Cells In Vivo and In the Perfused Mouse Liver.** (Eng) Roos, E. (Div. Cell Biology, Antoni van Leeuwenhoekhuis, Netherlands Cancer Inst., Sarphatistraat 108, Amsterdam, Netherlands); Dingemans, K. P. *In: The Macrophage and Cancer. Proceedings of the European Reticuloendothelial Society Symposium held in Edinburgh, September 12-14, 1977.* European Reticuloendothelial Society (Edinburgh, Scotland): 448 pp.; 216-224; 1977.

The behavior of Kupffer cells toward several tumor cell lines (mammary adenocarcinomas TA3/Ha and TA3/St, melanoma B16, lymphosarcoma MB VI A, and thymic leukemias GRSL-18 and GRSL-19) was studied after in vivo injection of the tumor cells in the portal system of mice or addition of these cells to a synthetic medium that perfused an isolated mouse liver. Within 30 min after their arrival into the liver, TA3 and B16 cells were partly or completely surrounded by thin, electron-lucent cell processes of Kupffer cells. Micrographs suggest that the tumor cells were surrounded by a thin rim of Kupffer cell cytoplasm that subsequently contracted to enclose part or all of the tumor cell. A dense material, probably containing lysosomal enzymes, was then released around the enclosed tumor cell and it was subsequently degenerated. These observations strongly suggest that the cells were phagocytized. For the TA3 and B16 cells, there was no difference in the percentage of partially or completely surrounded tumor cells after 30, 60, 90 or 120 min. The av percentage of the cell surface covered by the Kupffer cells was similar in all experiments with one tumor cell line also did not tend to increase with time. MB VI A GRSL cells were little affected by the Kupffer cells. The from the perfusion and in vivo experiments were similar. refs)

78-6527 **Effect of Parity on Recovery of Inappar Nodule-transformed Mammary Gland Cells Vivo.** (Eng) DeOme, K. B. (Dept. Zoology, Univ. Califor Berkeley, CA, 94720); Miyamoto, M. J.; Osborn, R. C.; G man, R. C.; Lum, K. *Cancer Res* 38(11, part 2): 4050-40 1978.

Inapparent nodule-transformed cells were recovered from late-pregnant BALB/cfC3H mice (5 first-pregnancy fema 4 mo old, 5 multiparous females 6-7 mo old) by a cell-c sociation technique, aliquots of 100,000 viable cells in 0 ml media were injected into the gland-free mammary fat pa of 3-wk-old syngeneic hosts, and the emergence of typi nodule outgrowths (LA's) was determined. Recovery of L indicated the presence of nodule-transformed cells in inoculum. The results were compared with those deriv previously from virgin BALB/cfC3H mice. The percenta of LA-type outgrowths (LS's, nodule-ductal outgrowths, a nodule-tumor outgrowths) derived from both donor grou was high: 63% and 45% for those aged 4 and 6-7 mo, resp tively. There was no correlation between the percentage LA's and donor age or number of litters born. Virgin mi of the same ages averaged 11% LA's. LA's were recover from all 10 of the parous donors, vs only 8/12 of the virg donors. Hyperplastic alveolar nodules (HAN) and tumo were not encountered in virgins < 8-9 mo old, whereas 36 of the parous females 4-5 mo old had overt HAN and 3.6 had tumors, and 73% of the parous females 8-9 mo old h overt HAN and 73% had tumors. The incidence of ove lesions was only 40% in virgins aged 12-14 mo. The da suggest that parity significantly increases the number nodule-transformed cells in donor tissue, decreases the tir required for the emergence of nodules and tumors, and i creases the number of overt nodules and tumors. (7 refs)

78-6528 **The Respiratory Epithelium. III. Histogenes of Epidermoid Metaplasia and Carcinoma Situ in the Human.** (Eng) Trump, B. F. (Dept. Patholog Univ. Maryland Sch. Medicine, 31 S. Greene St., Baltimor MD, 21201); McDowell, E. M.; Glavin, F.; Barrett, L. A Becci, P. J.; Schurch, W.; Kaiser, H. E.; Harris, C. C. *J Na Cancer Inst* 61(2): 563-575; 1978.

In an effort to test the hypothesis that epidermoid metaplasi (EMP) in the bronchial epithelium can result from direc conversion of columnar mucous cells to keratinizing epide moid cells, bronchial specimens of 100 patients with an without lung cancer were studied by light and electron m croscopy. Of the 71 lung cancer patients, 15 showed foc

P. The metaplastic epithelium was characteristically ıposed of basal cells overlaid by small mucous granule s (SMGC) that became progressively flattened toward the helial surface. Ciliated cells were absent. EMP showing nification was seen in only two specimens, both from can- patients. Epithelium showing mucous goblet cell hyper- sia and ciliated epithelium underwent abrupt transition to as of noncornifying metaplastic epithelium. Mucous gob- cell hyperplasia was seen in more than half of the speci- ns; a pattern of stratification was noted in some areas in -third of these hyperplasia specimens. Layers of SMGC s overlaid a row of basal cells, and the surface layer con- ed of cuboidal mucous goblet cells and/or SMGC. Stain- of metaplastic cells produced patterns similar to those of cosubstances in mucous goblet cells. Electron microscopy ther confirmed the mucous nature of these cell types. This dy emphasizes the differentiation potentialities of mucous ls that can divide and undergo goblet cell hyperplasia and IP. It is suggested that EMP and carcinoma in situ can ult from the conversion of mucous cells. (73 refs)

-6529 **Carcinoma of the Lung in a Drywall Taping Worker. Report of a Case.** (Eng) Fischbein, A. nvironmental Sciences Lab., Dept. Community Medicine, ount Sinai Sch. Medicine, City Univ. New York, Fifth Ave. d 100th St., New York, NY, 10029); Langer, A. M.; Suzu- Y.; Selikoff, I. J. *Toxicol Lett* 2(4): 231-236; 1978.

case of lung cancer in a 57-yr-old man who had been a avy smoker and a drywall taping worker for 25 yr is report- . Histologically, the tumor was a well-differentiated squa- ous cell carcinoma. Congestion of the pulmonary paren- yma, edema, bronchopneumonia, and pulmonary fibrosis ere also present. Numerous particles--sheet silicates, diatom agments, chrysotile asbestos fibrils, and unidentified crys- lline fibers--were observed throughout the lung tissue. The size of these particles was < 1 μm in greatest dimension. his case illustrates the importance of tissue analysis in the aluation of dust disease of the lung. (7 refs)

3-6530 **Giant Cell Transformation: Cerebrohepatorenal Syndrome.** (Eng) Carlson, B. R. (Dept. Patholo- , Children's Medical Center, 1935 Amelia, Dallas, TX, 5235); Weinberg, A. G. *Arch Pathol Lab Med* 102(11): 96-599; 1978.

male infant with cerebrohepatorenal syndrome of Zellwe- r was found, upon liver biopsy performed at 6.5 wk of age, have extensive hepatic giant cell transformation. In addi- on to features atypical of the early phase of the syndrome ere was widespread enlargement and multinucleation of patocytes. Upon autopsy at 16 wk, the liver showed early rrhosis and rare giant cells. Zellweger's syndrome may present another form of hepatic insult that may induce ant cell transformation. (19 refs)

78-6531 **Hepatoma Development During Long Term Follow-up Period of Liver Cirrhosis.** (Eng) Kobayashi, K. (First Dept. Internal Medicine, Sch. Medicine, Kanazawa Univ., Kanazawa, Japan); Kumagai, M.; Kameda, S.; Sugimoto, T.; Suzuki, K.; Nishimura, K.; Kato, Y.; Sugioka, G.; Hattori, N. *Acta Hepatogastroenterol (Stuttg)* 25(5): 344-349; 1978.

The relationship of hepatoma to liver cirrhosis was investigated, based on long-term (> 3 yr) follow-up studies of 20 Japanese patients with liver cirrhosis. Hepatoma was found at autopsy in 10/20 patients, all of whom had mixed-type cirrhosis. In the nonhepatoma group, two had micronodular cirrhosis and eight had the mixed type. The mean follow-up in the hepatoma and nonhepatoma patients was 5.5 and 5.0 yr, respectively. There were no heavy drinkers among the hepatoma patients, vs three in the nonhepatoma group. Blood samples were analyzed for hepatitis B surface antigen (HBsAg) and α_1-fetoprotein (FP) by radioimmunoassay, and localization and distribution patterns of HBsAg in the liver were determined by direct immunofluorescence and orsein staining. Six of the eight hepatoma patients tested were positive for HBsAg, vs 2/10 nonhepatoma patients. FP levels $>$ 20 mμg/ml were detected in 6/8 hepatoma patients tested, and in four of these patients they were > 300 mμg/ml. These results indicate that HBsAg-positive liver cirrhosis of the mixed type is closely related to hepatoma development in Japan. (12 refs)

78-6532 **Ultrastructural Features of Renal Carcinoma Cells.** (Rus) Dikshtein, E. A. (Dept. Pathological Anatomy, M. Gor'kii Donetsk Medical Inst., Donetsk, USSR); Vlodavskii, E. A.; Shevchenko, N. I.; Miima, J. G.; Merezhko, V. A. *Arkh Patol* 40(8): 10-16; 1978.

The ultrastructure of three renal cell carcinomas was studied. Two basic cell types were found. Clear cells, which predominated in these carcinomas, were characterized by a cytoplasm rich in lipid vacuoles and glycogen granules. Dark cells, which were scarce, contained small amounts of fat and glycogen but had well-developed mitochondria and other organelles. Both types of cells contained microvilli on the cell surface, desmosomes and interdigitations in the region of the cell contacts, and channels between the tumor cells. These features suggest that clear and dark cells have a common origin in the epithelium of the proximal tubules. (6 refs)

78-6533 **Mixed Endocrine Gastric Tumors Associated with Hypergastrinemia of Antral Origin.** (Eng) Larsson, L. I. (Inst. Medical Biochemistry, Univ. Aarhus, DK-8000 Aarhus, Denmark); Rehfeld, J. F.; Stockbrugger, R.; Blohme, G.; Schoon, I. M.; Lundqvist, G.; Kindblom, L. G.; Save-Soderberg, J.; Grimelius, L.; Olbe, L. *Am J Pathol* 93(1): 53-68; 1978.

Hypergastrinemia of antral origin associated with multiple mixed endocrine tumors of the gastric corpus mucosa occurred in a 57-yr-old diabetic woman. A screening test revealed serum gastrin levels of 4,000-5,000 picograms (pg)/ml (normal levels are < 100 pg/ml), and a pentagastrin test revealed achlorhydria. Upon gastroscopy, approx 20 polypous lesions were detected in the corpus mucosa. Following gastrectomy, serum gastrin levels decreased to < 10 pg/ml. Most (70%-80%) of the tumor cells were of the endocrine cell (so-called ECL cell) type, but enterochromaffin cells of various subtypes and agranular cells were also found. The tumors were locally invasive into the walls of submucosal blood vessels. The surrounding mucosa showed severe atrophic gastritis with intestinalization and contained numerous goblet cells, enterochromaffin cells, and cholecystokinin cells. The latter do not occur in normal oxyntic mucosa. Their presence in intestinalized gastric epithelium suggests that intestinalization also is associated with changes in endocrine cell populations. Gastrin exerts a trophic action on ECL cells. It is speculated that the primary lesion was achlorhydria; the subsequently raised serum gastrin levels, caused by decreased acid feedback inhibition, may have been instrumental in bringing about the hyperplasia and neoplasia of the ECL cells. (30 refs)

78-6534 **Adenocarcinoma of the Stomach with Common Variable Immunodeficiency Syndrome.** (Eng) Battle, W. M. (Section Gastroenterology, Dept. Medicine, Univ. Pennsylvania Hosp. and Sch. Medicine, 3600 Spruce St., Philadelphia, PA, 19104); Brooks, F. P. *Arch Intern Med* 138(11): 1682-1684; 1978.

Gastric adenocarcinomas developed as a late complication of the common variable immunodeficiency (CVI) syndrome in a man and a woman who were followed since age 27 and 30 yr, respectively. The syndrome was diagnosed on the basis of onset of disease in adolescence, no family history of increased susceptibility to infection, and little or no circulating IgG, IgA, or IgM. Atrophic gastritis and pernicious anemia were present in both patients. The anemia was characteristic of the CVI syndrome, with a defect in absorption of vitamin B_{12} and a lack of correction of the Shilling test after administration of intrinsic factor. In both cases, serum gastrin levels remained normal. Adenocarcinoma of the stomach was the most common epithelial tumor in a previous series of malignancies associated with the CVI syndrome. (18 refs)

78-6535 **Relationship Between Chronic Schistosomiasis Japonica and Carcinoma of the Large Intestine: Studies on 12 Cases of Adenocarcinoma of Large Intestine Associated with Eggs of *Schistosoma japonicum*.** (Jpn) Inoguchi, T. (First Dept. Surgery, Kurume Univ. Sch. Medicine, Kurume, Japan); Adachi, T.; Yamauchi, Y.; Isomoto, H.; Takamori, K.; Shinohara, M. *Igaku Kenkyu* 48(2): 93-100; 1978.

The relationship between chronic infection by *Schistoso japonicum* and carcinoma of the large intestine was inve gated. In 12 of 381 patients resected for colonic cancer cancer/parasite association was demonstrated histological mainly in the rectum and colon, with the stromal reacti in the mucosal or submucosal layer. However, a causal re tionship could not be proven. (42 refs)

78-6536 **Histogenesis of Malignant Transformation the Colonic Epithelium. A Detailed Study Semi-thin Sections.** (Eng) Mughal, S. (Dept. Histopatholo Westminster Medical Sch., London, England); Filipe, M. *Acta Gastroenterol Belg* 41(5/6): 215-225; 1978.

The histogenesis of colonic cancer was studied using semith (1 micron) resin sections of normal mucosa from 6 patien without gastrointestinal disease, adenomatous polyps and/ carcinomas from 11 patients with familial polyposis co (FPC), polyps from 8 patients without FPC, and 5 adenoca cinomas. For light microscopy, the sections were stained wi toluidine blue (TB), periodic acid-silver methenamin (PASM), PAS, high iron diamine (HID), and alcian blu (AB). The semithin sections revealed the gradations of ep thelial atypia from normal mucosa through adenoma to ca cinoma to the same degree as did electron microscopy (EM Goblet cell increases associated with changes in mucin secr tory products were shown by PASM. Vesiculated and ele tron dense bodies were visible with PASM and PAS stain and undifferentiated cells were easily identified with TB PASM. AB and HID highlighted variations in mucous secr tions in apparently normal mucosa adjacent to neoplasti growths. Other features indicative of epithelial dysplasia wer alterations in the basement cell membrane and microvilli an nuclear atypia. In FPC, the changes were more severe in th large polyps of the left colon and also in the polyps of th carcinoma patients. The advantages of semithin sections ove EM and routine histology in detecting early cancer are dis cussed. (12 refs)

78-6537 **Development of Cancer in Ulcerative Colitis** (Swe) Fredlund, P. (Kirurgiska kliniken, Lasa rettet, S-221 85 Lund, Sweden); Hoevels, J.; Petersson, B. G. Schain, M. *Lakartidningen* 75(40): 3539-3542; 1978.

Four patients (two men, two women, aged 29-48 yr) with ulcerative colitis developed colonic tumors. At surgery, two of the tumors were diagnosed as carcinomas and two as adenocarcinomas. Three patients also had peritoneal carcinomatosis. The interval between the diagnosis of ulcerative colitis and that of the colonic tumor was 12-20 yr in three cases, and approx 1 yr in the fourth. The incidence of colorectal cancer in ulcerative colitis is highest in the distal segment of the intestine. These cases confirm earlier observations on the increased incidence of colonic cancer in ulcerative colitis patients. (18 refs)

6538 **Heritable Colon Cancer and Solitary Adenomatous Polyps.** (Eng) Lynch, P. (Dept. Preventive licine, Creighton Univ., Omaha, NB); Lynch H.; Harris, Lynch, J.; Guirgis, H. *In: Prevention and Detection of ncer. Proceedings of the Third International Symposium on ection and Prevention of Cancer Held by the International dy Group for the Detection and Prevention of Cancer in v York, April 26 - May 1, 1976.* International Study Group the Detection and Prevention of Cancer. (New York,): Vol. 2(part 1), 2404 pp.; 1573-1589; 1978.

tudy was made of a large cancer-prone kindred character- l by a wide variation in age of onset of colon cancer and er a total lack or sporadic distribution of adenomatous yps in family members who developed colon cancer. Of approx 230 members in this kindred, 32 members have ortedly developed colonic and other gastrointestinal can- s. A striking trait expressed by this kindred is the inordi- e number of primary carcinomas occurring at the right on. Among the 24 patients whose tumor sites have been umented, the cecum was involved in 16 cases, the ascend- colon in 2, and the transverse colon in 4; only 2/24 had cer at only the descending or rectosigmoid colon. The idence of patients affected at the right colon is significantly ater than the highest reported figure for the general popu- on. Solitary adenomatous polyps were found in 13 colon ncer patients, but 7 had no polyps. The prevalence of syn- ronous and metachronous colon cancers was approx 50%, h additional primary cancers arising after segmental co- ic resection. The lack of an association between polyps and ncer in this kindred brings into question the role of enomatous polyps in malignant transformation. (19 refs)

-6539 **Histogenesis of Cloacogenic Carcinoma: Fine Structure of Anal Transitional Epithelium and oacogenic Carcinoma.** (Eng) Gillespie, J. J. (Dept. Ana- nic Pathology, Indiana Univ. Sch. Medicine, 1100 W. Mi- igan St., Indianapolis, IN, 46202); MacKay, B. *Hum Pa- ol* 9(5): 579-587; 1978.

ie fine structural morphology of the anal transitional zone described, and the ultrastructure of the two principal vari- ts of cloacogenic carcinoma is presented. The descriptions e based on histologic and electron microscopic evaluation eight cases of cloacogenic carcinoma (6 women, 2 men, -70 yr old) and tissue from four normal anorectal junctions. ial transitional epithelium is not highly specialized and in- rporates features of both urothelium and squamous epi- elium; slight urothelial differentiation is probably vestigial. ie transitional variant of cloacogenic carcinoma contained isters of small vesicles and Golgi complexes, indicating par- l differentiation. Histologically, the transitional variants sembled urothelial carcinoma but could be distinguished om it by numerous, well-formed desmosomes, frequent vil- lous projections, and a distinctly elongated form. The pleomorphic and basaloid variants differed from the transitional type chiefly in their relative lack of differentiation. The basaloid tumors resembled cutaneous basal cell carcinoma morphologically and probably represent undifferentiated basal cells originating within the basal layer of anal transitional epithelium. The cloacogenic basaloid tumor is highly metastatic. The observation of features of both urothelial and squamous structure in the transitional variant confirms that it is derived from the anal transitional zone, which also contains features of both structures. (21 refs)

78-6540 **Ovarian Fibromata in Four Successive Generations.** (Eng) Dumont-Herskowitz, R. A. (New England Medical Center Hosp., 171 Harrison Ave., Boston, MA, 02111); Safaii, H. S.; Senior, B. *J Pediatr* 93(4): 621-624; 1978.

Brief case reports are given for six ovarian fibroma patients from four generations of the same family. In two patients (21 and 42 yr old), the tumors were unsuspected until hysterectomies had been done because of uterine fibroids. In the remaining four patients (3-16 yr old), the tumors were large, multinodular, and calcified and were discovered before menarche. The tumors were bilateral in three subjects. No endocrine effects could be ascribed to any of the tumors. The distribution of ovarian fibromas in this family was very different from that usually observed. The tumors typically occur in an older age group and after menopause. They are multiple or bilateral in only 10% of the patients and calcified in only 8.5%. Many and possibly all female subjects, including adolescents, who suffer from the basal cell nevus syndrome have ovarian fibromas that are characteristically multinodular and calcified, but none of the patients in this family had any signs of this syndrome. The disorder in this family followed a dominant mode of transmission. The pattern was consistent with either autosomal sex-limited or X-linked sex-limited inheritance. (10 refs)

78-6541 **Characteristic Features of Hormonal Balance in Patients with Uterine Myoma.** (Rus) Arakeliants, A. B. (Dept. Obstetrics and Gynecology, Central Inst. Advanced Training Physicians, Moscow, USSR); Bakuleva, L. P. *Sov Med* (8): 140-144; 1978.

Changes in luteinizing hormone (LH), follicle-stimulating hormone (FSH), and somatotropic hormone (STH) levels were studied in 35 patients with uterine myoma (26 were 24-40 yr old, 9 were 40-45 yr old). On the basis of rectal temperature, 14 patients had a normal biphasic menstrual

cycle, 13 had a reduced second stage of the cycle (duration of the follicular phase was 19 days, duration of the luteinic phase was 8 days), and 8 patients had a monophasic basal temperature. In all the patients, there was no correlation between the peaks of LH and FSH, and there were additional peaks of LH and FSH during the first and second phases of the menstrual cycle. The patients with a deficient luteinic phase and an anovular menstrual cycle had a significantly decreased basal level of LH and FSH. All the patients had mildly decreased levels of STH. Fourteen patients had internal endometriosis, and a retrospective analysis revealed that these patients underwent (on av) 3.13 abortions, compared with 1.64 abortions in the patients without endometriosis. (18 refs)

78-6542 **Estimation and Correlation of High-Risk Factors for Cervical Carcinoma.** (Por) Do Carmo Fajardo Diestel, M. (Servico de Ginecologia, Faculdade Catolica de Medicina de Porto Alegre, Porto Alegre, Brazil); Dos Reis Peroni, R. *J Bras Ginecol* 85(5): 253-254; 1978.

Early sexual activity, young age at first childbirth, multiparity, and, especially, combinations of these criteria were identified as high-risk factors for cervical carcinoma in 28 patien (6 refs)

See also:

*(Rev.): 78-6034, 78-6049, 78-6055, 78-6059, 78-606
78-6061, 78-6062, 78-6063, 78-6064, 78-606
78-6066, 78-6068, 78-6069, 78-6070, 78-607
78-6072, 78-6073, 78-6074, 78-6075, 78-607
78-6085.

*(Chem.): 78-6120, 78-6135, 78-6136, 78-614
78-6157, 78-6191, 78-6195, 78-620
78-6211, 78-6222, 78-6235, 78-626
78-6276, 78-6280, 78-6332, 78-635
78-6354.

*(Phys.): 78-6363, 78-6364, 78-6375, 78-637
78-6378.

*(Viral): 78-6408, 78-6421, 78-6427, 78-6452, 78-645
78-6486.

*(Immun.): 78-6487, 78-6489, 78-6505.

*(Epid.-Biom.): 78-6543, 78-6547, 78-6549, 78-655
78-6565, 78-6573, 78-6575, 78-657

543 **Pre- and Postmenopausal Breast Cancer: Differences in Risk Factors.** (Eng) Vakil, D. V. t. Preventive Medicine and Biostatistics, Div. Comity Health, Univ. Toronto, Toronto, Ontario, Canada); gan, R. W. *In: Prevention and Detection of Cancer. Proings of the Third International Symposium on Detection Prevention of Cancer Held by the International Study up for the Detection and Prevention of Cancer in New , April 26 - May 1, 1976.* International Study Group for Detection and Prevention of Cancer. (New York, NY): 2(part 1), 2404 pp.; 1539-1550; 1978.

use of the possibility that pre- and postmenopausal st cancer represent two disease processes with different ogies, an attempt was made to identify risk factors that r between early- and late-onset breast cancer patients. A of 170 former breast cancer patients were identified the Toronto General Hospital tumor registry for -1971. Information of genetic, epidemiological, and paogical importance was elicited in an interview questione administered to all 170 women. Results of the survey ved that 61 patients were premenopausal and 109 were menopausal at the time of diagnosis. Analysis of risk fac revealed that high socioeconomic status and early age menarche were important in the development of menopausal breast cancer. Nulliparity, age at first pregcy, and weight-height index were more important in the elopment of postmenopausal breast cancer. In addition, gher proportion of premenopausal patients (38%) had a ily history of breast cancer, compared with the postopausal patients (22%). Thus, genetic factors are more ortant in the etiology of premenopausal breast cancer. (24)

6544 **Endocrine Status in Normal British, Japanese and Hawaiian-Japanese Women.** (Eng) Hayd, J. L. (Breast Unit, Guy's Hosp., London SE1 9RT, gland); Greenwood, F. C.; Glober, G.; Stemmerman, G.; brook, R. D.; Wang, D. Y.; Kumaokas, S. *Eur J Cancer* 11): 1221-1228; 1978.

e hypothesis that there are no major differences in endone function among women with Japanese ancestry in Hai, Japanese women, and British women that would acnt for the differences in breast cancer incidence among se racial groups was investigated. Women were divided o three menstrual groups based on menopausal status. ere were no differences in plasma and urinary estrogens ong premenopausal women of the three racial groups. The nopausal Hawaiians had a higher plasma and urinary esne level and a lower plasma progesterone level than British or Japanese women. In postmenopausal Hawaiian women, plasma estradiol levels were significantly lower than those in the other two groups. The differences in androgen status were very complex: plasma androstenedione and urinary 11-deoxy-17-ketosteroid and etiocholanolone levels were lower in Hawaiian than British women and resembled those in Japanese women, but plasma dehydroepiandrosterone levels were higher in Hawaiians than in Japanese and resembled those in British women. This study reinforces the conclusion that ovarian and pituitary hormone levels do not explain the differences in incidence of breast cancer among the three groups and suggests that changes of environment bring about some alterations of endocrine function, mainly in the androgens. (39 refs)

78-6545 **Cancer of the Brain in Hawaii.** (Eng) Korsak, R. K. (Cancer Center Hawaii, Univ. Hawaii, Honolulu, HI); Rashad, M. N. *In: Prevention and Detection of Cancer. Proceedings of the Third International Symposium on Detection and Prevention of Cancer Held by the International Study Group for the Detection and Prevention of Cancer in New York, April 26 - May 1, 1976.* International Study Group for the Detection and Prevention of Cancer. (New York, NY): Vol. 2(part 1), 2404 pp.; 2225-2228; 1978.

The incidence of malignant brain tumors in Hawaii was studied for two periods, 1960-1964 and 1968-1972. Age-specific incidence rates and age-adjusted rates were computed by sex and race (Caucasian, Chinese, Filipino, Hawaiian, and Japanese). There was a total of 162 brain tumors: 68 occurred during the first period, 94 during the second period. The age/race-incidence rates were 1.9/100,000 women and 2.2/100,000 men for the early period. During the later period, the incidence was 2.2/100,000 women and 2.7/100,000 men. There appeared to be significant racial differences, with Caucasians and Hawaiians having higher incidence rates than the other racial groups. Mortality due to malignant brain tumors was highest among Caucasian men and Hawaiian women. These results confirm the gradient between Caucasians and Orientals for brain tumors. (11 refs)

78-6546 **Cancer among Hawaiians and Part-Hawaiians.** (Eng) Rashad, M. N. (Dept. Genetics, Cancer Center Hawaii, Univ. Hawaii, Honolulu, HI); Mi, M. P.; Budy, A. M. *In: Prevention and Detection of Cancer. Proceedings of the Third International Symposium on Detection and Prevention of Cancer Held by the International Study Group for the Detection and Prevention of Cancer in New York, April 26 - May 1, 1976.* International Study Group for the Detec-

tion and Prevention of Cancer. (New York, NY): Vol. 2(part 1), 2404 pp.; 2209-2218; 1978.

Cancer incidence among Hawaiians and part-Hawaiians was analyzed for the period 1968-1972. Of the total 1,057 cancer patients, 465 were women and 592 men. Age-specific and age-adjusted incidence rates were computed for selected sites. The age-adjusted av annual incidence rate per 100,000 was 243.6 for men and 258.1 for women. The most common cancer in men was cancer of the lung, which accounted for 25% of all cases, followed by cancer of the stomach (8.6%). In women, the most frequent cancers were cancer of the breast (21.3%) and cervical cancer (17.2%). Comparison with other racial groups (Caucasian and Japanese) showed that Hawaiians and part-Hawaiians have the highest incidence rate of cancer of the lung and of the corpus uteri. This study confirms earlier reports of an excess of cancer among Hawaiians and part-Hawaiians. (30 refs)

78-6547 **Contribution to the Problem of the Association of Silicosis and Lung Carcinoma.** (Ita) Cardesi, E. (Servizio di anatomia e istologia patologica, Ospedale San Luigi Gonzaga di Orbassano, Turin, Italy); Provana, A. *Pathologica* 70(1005/1006): 377-401; 1978.

Data on 204 patients with silicosis and/or pulmonary carcinoma diagnosed at autopsy or by postoperative histological examination at an Italian Hospital during 1975-1976 were tabulated and analyzed. Age, sex, profession, tumor histology and site, type of silicosis, and the carcinoma-silicosis association were considered. There were 135 patients with pulmonary carcinomas (116 men aged 34-81 yr and 19 women aged 50-81 yr). These tumors were subdivided into epithelial carcinoma (49 men, 3 women), microcytoma (17 men, 3 women), adenocarcinoma (18 men, 5 women), anaplastic and large cell carcinoma (26 men, 3 women), and bronchial-alveolar carcinoma (6 men, 5 women). The most frequent sites were the superior (60/135) and inferior lobes (34/135). Of the 32 silicosis patients, 29 were men (aged 40-80 yr) and 3 were women (aged 44-61 yr). Silicosis was classified as massive (10 men, 2 women), nodular (8 men, 1 woman), and peribronchial-vascular (11 men). Thirty-seven patients had both conditions (34 men aged 41-80 yr and 3 women aged 62-80 yr). The most frequent sites for silicosis-carcinoma were superior lobe (15/37), inferior lobe (12/37), and principal bronchus (5/37). Epithelial carcinomas were most common, and they were associated with all types of silicosis: massive (3/37), nodular (5/37), and peribronchial-vascular (7/37). Because of a lack of information, no statistically valid conclusions could be drawn on the association of various professions with silicosis or carcinoma. No statistically valid correlation could be made between the type of silicosis and the histological type of carcinoma. An indirect causal relationship may exist between silicosis and pulmonary carcinoma. (36 refs)

78-6548 **Epidemiologic Studies of Cancer in Man Animals Sharing the Same Environment.** (
Schneider, R. (Animal Neoplasm Registry, Dept. Epid ology and Preventive Medicine, Univ. California, Sch. Ve nary Medicine, Davis, CA, 95616). *In: Prevention and D tion of Cancer. Proceedings of the Third Internati Symposium on Detection and Prevention of Cancer Hel the International Study Group for the Detection and Pre tion of Cancer in New York, April 26 - May 1, 1976.* Inte tional Study Group for the Detection and Prevention of cer. (New York, NY): Vol 2(part 1), 2404 pp.; 1377-1 1978.

The patterns of human and animal cancer in the same e ronment were examined by comparing the incidence r and sex pattern for the major sites of cancer found in hum dogs, and cats in two California counties: Alameda and C tra Costa. Animal ages were converted to human age-equ lents, and both the human and animal crude incidence r were age-adjusted to the same population age distributio determined by the 1950 US census. Human cancer rates w at least threefold higher than dog or cat rates for six si lung, bladder, digestive tract, prostate, ovary, and ute Possible reasons for these excess cancers are given. Ca rates were threefold higher in the gum and testis, and fe rates were threefold higher for leukemias and lymphon Sex rate ratios for cancer showed excess male cases for mans and cats and excess female cases for dogs. Sex ra at specific sites indicated better agreement between hum and cats than between humans and dogs. Comparison of c cer occurrence in three species under similar conditions m help elucidate how cancer is expressed at specific sites. refs)

78-6549 **Association of Squamous Cell Carcinoma of t Head and Neck with Cancer of the Esophag** (Eng) Goldstein, H. M. (Dept. Diagnostic Radiology, Un Texas System Cancer Center, M.D. Anderson Hosp. and T mor Inst., 6723 Bertner Ave., Houston, TX, 77030); Zo noza, J. *Am J Roentgenol* 131(5): 791-794; 1978.

The association between esophageal cancer and squamo cell carcinoma of the head and neck region (oral cavity, ph rynx, and larynx) was studied by reviewing hospital files f the period March 1944 to August 1976. Eight-nine patien were found who had separate primary squamous cell tumo of the head and neck and of the esophagus, representing 10 of all patients with esophageal carcinoma evaluated at th institution. In >80% of the patients, the separate prima tumors were discovered asynchronously (2 mo-16 yr apart The expected number of esophageal carcinomas among th 10,000 patients with head and neck cancer was 10, compare with the 89 observed. The number of second primary tumo of the stomach and colon among the head and neck canc population was not greater than anticipated. Most patien

a longstanding history of considerable cigarette and al-
l use. These findings suggest that alcohol and tobacco
tiologic factors linking these two primary cancer groups,
they indicate the importance of complete radiological
uation of the esophagus in head and neck cancer patients.
efs)

6550 **Fluoridation of Water Supplies and Cancer - A Possible Association?** (Eng) Oldham, P. D. RC Pneumoconiosis Unit, Llandough Hosp., Penarth, S. morgan, Wales); Newell, D. J. *J R Stat Soc Ser C* 2): 125-135; 1977.

a from a recent study of the crude cancer mortality rates 0 US cities with fluoridated water supplies and 10 US s with nonfluoridated water were reexamined to deter-e whether the conclusion that nationwide fluoridation ld lead to excess cancer deaths was justified. At the begin-g of the study (1950), the cities with fluoridated water had er elderly white men and women, more nonwhites aged 0 yr, and a greater proportion of cancer deaths than those h nonfluoridated water. At the end of the study, the cities h fluoridated water had many more nonwhites of all ages fewer whites aged <55 yr than those with nonfluoridated er. Taking these variables into account, the excess cancer e increased by 1% over the study period in the cities with oridated water and by 4% in those with nonfluoridated er. In absolute terms, the excess cancer rate between 1950 1970 increased by 8.8/100,000 in those with non-oridated water. It is concluded that the study provided no dence that fluoride increases cancer mortality. (7 refs)

6551 **Cancer Epidemiologic Surveillance in the Du Pont Company.** (Eng) Pell, S. (Medical Div., E. duPont de Nemours and Co., Wilmington, DE, 19898); Berg, M. T.; Karrh, B. W. *J Occup Med* 20(11): 725-740; 78.

e surveillance program started at the Du Pont Company 1956 is described, and employee morbidity and mortality tistics are presented for the period 1956-1974. With certain eptions, age-specific cancer incidence and mortality ratios re lower than those found in the Third National Cancer rvey. For men, the incidence ratio for all forms of cancer s 79 and the mortality ratio was 82. The corresponding ios for women were 111 and 82. Mortality differences be-een Du Pont and the US decreased with increasing age. e incidence of malignant skin melanoma in men was sig-icantly higher than expected, based on NCI data (Standard cidence Ratio, SIR = 123, $P<0.05$). The magnitude of e excess was slightly higher in salaried men (SIR = 127) an in wage role employees (SIR = 121). A significant ex-ss of intestinal cancer occurred in salaried men employees IR = 117, $p<0.05$). Among women, cervical cancer inci-nce was significantly higher than expected (SIR = 233, $p<0.05$), and it was especially high among the wage roll employees (SIR = 296). Breast cancer incidence was significantly higher in salaried employees (SIR = 136, $p<0.05$), but was lower than expected in wage roll employees (SIR = 81, $P<0.05$). Among salaried women employees, there were 11 cases of leukemia, which was significantly greater than the expected 6.1 ($p<0.05$). Primary sites for which the incidence rates were especially low were for men: the thyroid, larynx, prostate, and buccal cavity, and pharynx; and for women, the lung. Cancer morbidity and mortality rates for the entire company cannot be relied on to indicate an increased risk of cancer resulting from exposure to a particular carcinogenic substance in the company. (16 refs)

78-6552 **Nasopharyngeal Carcinoma Patients in Massachusetts.** (Eng) Goodman, M. L. (Dept. Otolaryngology and Pathology, Massachusetts Eye and Ear Infirmary, James Homer Wright Pathological Lab., Massachusetts General Hosp. and Harvard Medical Sch., Boston, MA); Levine, P. H.; Miller, D. *In: Prevention and Detection of Cancer. Proceedings of the Third International Symposium on Detection and Prevention of Cancer Held by the International Study Group for the Detection and Prevention of Cancer in New York, April 26 - May 1, 1976.* International Study Group for the Detection and Prevention of Cancer. (New York, NY): Vol. 2(part 1), 2404 pp.; 1591-1598; 1978.

Possible etiological mechanisms of genetic susceptibility and Epstein-Barr virus (EBV) infections in nasopharyngeal carcinoma (NPC) were investigated. Thirty patients treated for NPC from 1972 to 1975 and controls matched by age (within 5 yr), race, sex, and level of education were evaluated for antibodies to EBV viral capsid antigen (VCA) and early antigen (EA). In addition, patients and controls were questioned about their personal habits and dietary practices. The two groups did not differ in the proportion of individuals reporting the use of coffee, tea, alcoholic beverages or cigarettes, although the NPC patients were heavier smokers than the controls (47% vs 22%, respectively, smoked 2 packs or more per day). VCA antibody determinations varied from 1:160 to 1:2560 for NPC patients and 1:40 to 1:1280 for controls, with respective median values of 736 and 370. EA antibody levels were also higher in NPC patients, 13/26 patients having titers of 160 and above, compared with 2/27 controls. Elevated VCA and EA antibodies, low socioeconomic status and heavy smoking habits were the most frequent consistent findings in the NPC group. (4 refs)

78-6553 **Incidence Rates and Risk Factors of Benign Breast Neoplasms.** (Eng) Cole, P. (Dept. Epidemiology, Harvard Sch. Public Health, 677 Huntington Ave., Boston, MA, 02115); Elwood, J. M.; Kaplan, S. D. *Am J Epidemiol* 108(2): 112-120; 1978.

A case-control study of benign breast disease was conducted in the Greater Boston area during 1968-1969. The cases were 938 women initially diagnosed as having fibrocystic disease (FD), fibroadenoma (FA), or a mixed lesion (ML) during the 18-mo study period. Controls were a random sample of the entire reference population. Mailed questionnaires were completed by 678/938 benign breast disease women and 1,807/2,062 controls contacted. Information on factors known to be related to breast cancer was obtained, to allow the similarities of the two conditions to be assessed. The age-standardized incidence rate for FD and FA was 89.4 and 32.8 per 100,000 woman-yr, respectively. The incidence of FD rose to age 45 and then declined sharply, that of FA peaked during the 20's, and that of ML had a mode at age 30-34. Among young women, the highest rates occurred in married nulliparae, but this was not so at higher ages. The incidence of FD and FA did not follow a pattern consistent with parity or age at first birth. The risk of FA increased with late age at menarche and that of FD increased with later natural menopause and with artificial menopause at any age. The risk of FD, but not of FA, also increased in women with arthritis and women in higher socioeconomic groups. The relative incidence of all three benign breast diseases decreased steadily with increasing obesity. The epidemiologic pattern of FD and FA did not correspond to that of breast cancer, which is directly related to obesity but not to age at menarche or to artificial menopause. Previous studies have indicated that the risk of breast cancer in benign disease may be limited to conditions such as severe ductular atypia or carcinoma in situ. (25 refs)

78-6554 **Radiation, Smoking and Height Relationships to Lung Cancer in Uranium Miners.** (Eng) Archer, V. E. (Natl. Inst. Occupational Safety and Health, Center Disease Control, US Dept. Health, Education and Welfare, 390 Wakara Way, Salt Lake City, UT, 84108). *In: Prevention and Detection of Cancer. Proceedings of the Third International Symposium on Detection and Prevention of Cancer Held by the International Study Group for the Detection and Prevention of Cancer in New York, April 26 - May 1, 1976.* International Study Group for the Detection and Prevention of Cancer. (New York, NY): Vol. 2(Part 1), 2404 pp.; 1689-1712; 1978.

A prospective mortality study using a life table method was done on 3,366 white underground uranium miners and 1,231 surface workers. Cumulative radon daughter exposure values were calculated for each miner from the date of his first mining to each sequential month of observation through September 1969. Miners were classified into tobacco groups on the basis of cigarette use only. Observed deaths exceeded those expected from respiratory cancer (146 vs 30), pneumoconiosis and related diseases, and accidents related to work. The overall rate of death from respiratory cancer among the miners was 4.9 times greater than that expected from general population data and 6.0 times greater than that found among the control group of surface workers. Exposure-response relationships with radiation varied with the height of the w ers, cigarette smoking, and latent period between start of ing and disease. Of the four factors involved in malignant and nonmalignant respiratory diseases (he free silica, cigarette smoking, and alpha radiation), radia was the most important. The clinical observation that s uranium miners have more lung disease than larger mi was substantiated by the data gathered in this study. Mi are engaged in physical labor, and tall men have larger lu so it is postulated that short miners receive a higher dos noxious agents per unit of lung tissue when performing e work. It is concluded that standards for airborne nox agents should consider the amount of physical labor invol and the size of individual workers. (20 refs)

78-6555 **A Comparison Model Approach to the Esti tion of Tumor Incidence and Growth: Invest tion of a Model of Cancer Latency.** (Eng) Tolley, H. (Dept. Statistics, Texas A & M Univ., College Station, 77843); Burdick, D.; Manton, K. G.; Stallard, E. *Biomet* 34(3): 377-389; 1978.

The nature of cancer, with its lengthy latent period, ma collection of data on the entire process of carcinogenesis ficult, as the early rate and pattern of tumor growth are un served. Stochastic compartment modeling is proposed solve the problems of estimating the transition probabili of a partially observed stochastic process. The goal of model is to synthesize the results of various studies int coherent model of cancer latency and general population i dence of cancer. The rate coefficients for a time-depende multiple compartment system were estimated for cancer-s ceptible and nonsusceptible portions of a population, w individual rate coefficients being identified as explicit fu tions of age and tumor growth times. Under the model tumor latency is relatively lengthy and if the population be studied is elderly, many tumors may not become clinica manifest due to mortality from other diseases. Susceptibil affects the model by fixing the proportion of persons who m get cancers. The model, with parameters representing tum incidence, time to tumor death given onset, genetic suscep bility to tumor growth, and the effects of competing forc of mortality, was fitted to data on 1969 deaths due to stoma cancer for US men aged ≥ 25 yr. Two forms, one with waiting time distribution for occupants of the latent state a one with a single latency time, achieved excellent fits to t data. (33 refs)

78-6556 **Associations of Cancer Mortality with Halom thanes in Drinking Water.** (Eng) Cantor, K. (Health Effects Res. Lab., U.S. Environmental Protecti Agency, Cincinnati, OH, 45268); Hoover, R.; Mason, T. McCabe, L. J. *J Natl Cancer Inst* 61(4): 979-985; 1978.

Age-standardized cancer mortality rates by site and sex f

tes in 76 US counties were compared with levels of chlo-
rm, bromine-containing trihalomethane(s) (BTHM), and
l trihalomethane(s) (THM) in the drinking water. The 76
nties are >50% urban, and over half the population is
ed by a sampled water supply. Using several demograph-
socioeconomic, and industrial variables, a predicted mor-
y rate was computed and compared with the actual rate.
resulting residual mortality rate for each county was
pared with the level of one of the three THM indicators
use of the bivariate correlation coefficient. Counties were
uped according to the overall percentage of the county
ed by the sampled water supply (low, intermediate, or
h) and by geographic location. Bladder cancer residual
rtality in both sexes showed a strong correlation with
HM. This correlation persisted in spite of controls for so-
class, ethnic group, urban vs rural residence, presence of
cific high-risk industries, and lung cancer rates (possible
rogate for levels of cigarette smoking). Brain cancer was
correlated in both sexes, but the associations were not
strong, and there was regional variation. Other sites that
e indications of an association were: $CHCl_3$ levels and
le kidney cancer, BTHM and female lung cancer, and
M levels and non-Hodgkin's lymphoma in men. Stomach
ncer in women showed a negative correlation. (23 refs)

-6557 **A Critique of the Statistical Evidence Associating Estrogens with Endometrial Cancer.** (Eng) nstein, A. R. (Dept. Medicine, Yale Univ. Sch. Medicine, w Haven, CT, 06510); Horwitz, R. I. *Cancer Res* 38(11, t 2): 4001-4005; 1978.

veral types of bias that may have influenced the estro-
n-endometrial cancer (E-EMC) association are described.
postmenopausal women with EMC, detection bias is pro-
ced because of the dilation and curettage or other diagnos-
tests ordered when bleeding occurs as a side effect of E
rapy. These tests allow the detection of EMC's that might
nerwise be silent and undetected in women who do not take
The problems of detection bias have been ignored in most
se-control studies and they are difficult to deal with, as the
s occurs before cases and controls enter the study. To
luce this bias, the conventional method of epidemiological
ection must be altered. Instead of two individual groups
ng chosen, both cases and controls can be selected from
ingle sampling frame consisting of people referred for per-
rmance of the particular diagnostic test used to identify the
get disease. The bias can be reduced further by stratifying
tients according to the cogent clinical reason that led to
eir referral to the hospital for the diagnostic test. Other
urces of bias for the E-EMC association include the inad-
rtent prescription of E's for women with unrecognized
MC, the absence of double-blind interviewing techniques,
d arbitrary definitions of exposure to E's. The current con-
oversy about E's and EMC is a result of the inadequate
ality of conventional methods used for epidemiological re-
arch in chronic disease. (18 refs)

78-6558 **Geographic Patterns of Prostate Cancer in the United States.** (Eng) Blair, A. (Environmental Epidemiology Branch, Div. Cancer Cause and Prevention, NCI, NIH, Bethesda, MD, 20014); Fraumeni, J. F. *J Natl Cancer Inst* 61(6): 1379-1384; 1978.

Age-adjusted rates of mortality from prostate cancer during 1950-1969 were correlated by race with demographic, industrial, and agricultural data from 3,056 US counties. Prostate cancer was rare in young whites and nonwhites, increased progressively after 35 yr of age, and reached a plateau after 75 yr of age. Among whites, mortality rates in the midwest and northcentral regions were significantly higher than the total US rate, but the relative difference between the lowest and highest regional rates was only 8%, which is considerably less variation than that seen among whites with other tumors. Mortality among nonwhites was 50% higher than that among whites in all parts of the country where blacks comprise most of the nonwhite population. The rising rate associated with population density among nonwhites, but not whites, suggests that environmental exposures related to urban living may account for the predisposition of American blacks to prostate cancer. Mortality was elevated in counties with a high percentage of residents of Scandinavian descent, consistent with the high incidence reported for Sweden, Norway, and Denmark. Mortality was also elevated in counties with metal-using and textile industries and in regions with high consumption of high-fat foods. (46 refs)

78-6559 **Colon Cancer in a Low-Risk Population.** (Eng) Lyon, J. L. (Dept. Family and Community Medicine, Univ. Utah Coll. Medicine, Salt Lake City, UT, 84132); Sorenson, A. W. *Am J Clin Nutr* 31(10): S227-S230; 1978.

Colon cancer (CC) incidence from 1966 to 1970 was studied for the state of Utah, which had a CC mortality 34% below the US av during 1950-1969. The 10,641 cancer cases over this 5-yr period were compared to the age incidences of the Third National Cancer Survey (TNCS), broken down as to religious group (6,412 were Mormons), and computed as standard incidence ratios (SIR). The overall cancer SIR for the Mormon population was 75.6; for the non-Mormons, 93.9. For CC specifically, the corresponding SIR was 62.9 and 81.6, respectively. Mormons had a significantly lower risk of cancer of esophagus and lung than non-Mormons, due presumably to their religious ban on tobacco and alcohol. Furthermore, Mormon women had cancer incidence rates significantly lower than TNCS values at the colon-correlated sites of corpus uteri, breast, and ovary. Because per capita beef consumption in Utah is greater than the national average, and the anatomic distribution of colon cancer was not different between religious groups, Utah Mormons do not seem to adhere to a vegetarian diet. This conclusion, coupled with the low incidence of colon cancer, does not support the current hypothesis relating meats, fats, and dietary fiber to colonic cancer. (18 refs)

78-6560 **Mortality in Unionized Truck Drivers.** (Eng) Luepker, R. V. (Lab. Physiological Hygiene, Stadium Gate 27, Univ. Minnesota, Minneapolis, MN, 55455); Smith, M. L. *J Occup Med* 20(10): 677-682; 1978.

Mortality rates among 184,435 male members of the Central States Teamsters Union during May-July 1976 were determined by surveying death certificates issued during that period and then comparing them with the rates for the general US population (GP). In this period, 249 deaths occurred, with the two leading causes being cardiovascular disease (104) and cancer (72). Except for respiratory tract cancer and motor vehicle accident deaths, mortality rates were lower than those in the GP and comparable to those in other employed populations. The mortality rate for all cancers paralleled and was not significantly different from that found in the GP. Respiratory tract cancers, mainly cancer of the lung, were the leading cause of death in the cancer category, accounting for 48% of the cases. Respiratory tract cancer mortality among the teamsters was in slight excess at ages 40-49 and 60-69 and significantly higher at ages 50-59 than that in the GP. It was not possible to separate the effect of cigarette smoking from environmental exposure to explain the excess respiratory tract cancer mortality. (12 refs)

78-6561 **Occupational Cancer in Chromium Factory Workers.** (Jpn) Sano, T. (Dept. Pathology Occupational Diseases, Inst. Science Labor, Kawasaki-shi, Kanagawa Prefecture 213, Japan); Ebihara, I. *Jpn J Chest Dis* 37(2): 91-101; 1978.

Inflammation and cancer of the skin and mucosa of respiratory tract organs and, also, organs of the digestive tract have been found in chromium factory workers. These lesions are caused by the interaction of Cr and nickel, carcinogenic and inflammatory agents that infiltrate into the body during Cr production, with manganese and vanadium, inflammatory agents. Trivalent Cr plays a leading role in chronic inflammation and carcinogenesis. As of August 1975, there were 17 deaths due to lung cancer, 21 due to cancer of the respiratory organs, and 11 due to cancer of other organs (3 stomach cancers, 4 liver cancers, 1 neck sarcoma, 1 acute lymphatic leukemia, 1 reticulum cell sarcoma, and 1 renal cancer) among former Cr factory workers. Continued inflammatory stimulation induces repeated degeneration and regeneration of cells, leading to instability of the intranuclear gene and, hence, formation of an acquired factor for carcinogenesis. (27 refs)

78-6562 **Cancer Epidemiology. Series No. 7: Solid Lymphomas in New South Wales.** (Eng) Ford, J. (Central Cancer Registry, Health Commission of NSW, GPO Box 4235, Sydney, New South Wales 2001, Australia). *Cancer Forum* 14: 111-114; 1978.

The incidence of solid lymphomas in New South Wal 1972 was investigated using data from the New South V Statutory Cancer Notification Form. Solid lymphoma clude all cancers classified as lymphosarcomas, reticulun sarcomas, Hodgkin's disease, giant follicular lympho mycosis fungoides, and other malignant lymphomas, in ing those originating in organs other than lymph node 1972, the incidence of new cases was 246 for men (5% of cancers) and 212 for women (4% of new cancers). The dence of solid lymphomas is greatest in the older age gr (70 yr and over). There were 288 deaths from this canc 1972: 163 in men and 125 in women. There is no evid that the lymphomas are transmitted by close personal tact. (no refs)

78-6563 **High Incidence of Metalworkers among tients with Testicular Cancer.** (Eng) Rhoml W. (Dept. Radiotherapy and Special Oncology, Sch. M cine, Hannover, W. Germany); Schmoll, H. J. *In: Preve and Detection of Cancer. Proceedings of the Third Int tional Symposium on Detection and Prevention of Cancer by the International Study Group for the Detection and vention of Cancer in New York, April 26 - May 1, 1976.* I national Study Group for the Detection and Preventio Cancer. (New York, NY): Vol. 2(Part 1), 2404 1737-1743; 1978.

Forty-five patients who had undergone radiation therap a malignant testicular tumor in 1969-1974 were intervie to obtain occupational and medical histories. The orig diagnoses were as follows: 27 seminomas, 8 teratocarcino 5 embryonal cell carcinomas, and 5 mixed forms. Nine of the patients were skilled metalworkers, and an additi seven patients had formerly been employed in this indu The group of metalworkers included locksmiths, moldn ers, turners, car mechanics, electromechanics, and tool n ers. Occupational exposure to metal compounds or m dust ranged from 4 to 24 yr. Of the 19 nonmetalworker had a history of exposure to metals (for 2-26 yr) that related directly or indirectly to their occupation, and other patients were exposed to metals as a result of a hob Only 9/45 patients showed no overt exposure to metals ing for several years. (11 refs)

78-6564 **Soft-Tissue Effects Following ^{224}Ra Injecti into Humans.** (Eng) Spiess, H. (Kinderpo linik, Universitat Munchen, Munich, W. Germany); C spach, A.; Mays, C. W. *Health Phys* 35(1): 61-81; 1978

The soft-tissue effects of iv injections of radium-224 for treatment of tuberculosis, ankylosing spondylitis, and s other diseases were investigated in 204 patients treated juveniles (1-20 yr old) and 612 treated as adults. Dosage injection span were known in all patients. The av follow time from the first injection was 17 yr for the adults and

or the juveniles. Eighteen men injected as adults and two juveniles developed neoplasms, compared with 25 expect- Seventeen women injected as adults and three as juveniles eloped cancer, exceeding the eight expected cases. Howev- when the male and female cases were combined, the 38 s observed agreed closely with the 33 expected, suggest- that most of the soft-tissue neoplasms appearing so far e naturally occurring rather than related to ^{224}Ra therapy. tain types of malignancy did occur at a rate above the ected value: leukemia (2 observed vs 0.8 expected), breast cer (5 vs 1.2-1.8 expected), and renal cell carcinoma (3 0.6-1.1 expected), which suggests that they might have n radiation-induced. More may appear later because of the g latent period characteristic of radiation-induced cancer umans. (41 refs)

6565 **Soft Tissue Sarcomas and Intramuscular Injections: An Epidemiological Survey.** (Eng) McIllray, M. B. (Univ. Dept. Therapeutics, City Hosp., Nottham NG5 1BB, England); Langman, M. J. *Br Med J* 141): 864-865; 1978.

ords of patients presenting with soft tissue sarcomas dur- 1974-1975 in the Trent, England, area were analyzed to ermine whether the tumor could have been the result of vious im injections of iron preparations. Of 46 traceable ents with tumors on the leg, 12 had tumors at sites where ctions might have been given, but only 2 cases rose specifi- y in the buttock. Records of all 46 patients were investi- d, and no history of allergy, iron deficiency, or previous tment by injections of any sort was noted. Likewise, of raceable patients with sarcomas on the arm, 5 had tumors n area where injections might have been given, but all 19 ords proved negative for the types of information sought. se findings, therefore, do not support the suggestion of usual relationship between sarcoma formation and im in- ions of iron or other preparations. (5 refs)

6566 **Frequent Elevation of Tissue Polypeptide Antigen in the Sera of Workers Exposed to Bladder cinogens.** (Eng) Kumar, S. (Christie Hosp. and Holt lium Inst., Withington, Manchester M20 9BX, England); son, P.; Brenchley, P.; Taylor, G.; Bjorklund, B.; Eklund, *Int J Cancer* 22(5): 542-545; 1978.

vated levels of tissue polypeptide antigen (TPA), a sub- ce purified from human tumors and placenta, have been nd in sera from cancer patients. The diagnostic, prognos- or epidemiological significance of sequential determina- s of serum TPA levels was evaluated by comparing the lts of these determinations in 108 male chemical workers osed for at least 6 mo to 1-naphthylamine, 2-naphthyla- e, benzidine, or a combination of these chemicals; 26 dder cancer patients; and 63 healthy men. TPA was es- ated by a hemagglutination-inhibition technique. The proportion of individuals with a raised TPA level among the workers and patients was significantly higher (40/108 and 11/26) than that among the normal men (6/63). However, there was no significant difference in the proportion of positives between the workers and patients. It is suggested that a raised serum TPA level may be a very early indicator of hyperplastic bladder epithelium. (18 refs)

78-6567 **Management of Urinary Bladder Cancer.** (Eng) Fichardt, T. (Dept. Radiotherapy, H. F. Verwoerd Hosp., Pretoria, S. Africa); Sandison, A. G. *S Afr Med J* 54(18): 731-740; 1978.

From 1960 to 1976, 231 patients (198 men, 33 women) with primary cancer of the bladder were referred to a South African Hospital, and the etiology and clinicopathology of this disease are surveyed based on analyses of these patients and the literature. There were 115 transitional cell carcinomas, 87 anaplastic carcinomas, 15 squamous cell carcinomas, 12 papillary carcinomas, and 2 adenocarcinomas among the study group. Most (90%) of the patients presented with hematuria alone; the others presented with hematuria plus frequency and dysuria, incontinence, and bladder calculi. The duration of symptoms ranged from 2 wk to 2 yr, but most lasted 3-6 mo before diagnosis. The lesions were mostly single, situated mainly on the lateral and posterior walls and on the trigonum. Predisposing factors are numerous and varied, but cigarette smoking poses the greatest hazard for the general population. Cigarette smoking blocks the normal metabolism of tryptophan, leading to an accumulaton of carcinogenic metabolites of tryptophan in the urine. The basic abnormality is an inability to convert 3-hydroxyanthranilic acid to nicotinamide. Other possible etiologic agents include the aromatic amines used in the dyestuff, rubber, and plastic industries; pesticides, especially those containing naphthylamines; dyes used in the manufacture of foods, cosmetics and drugs; bilharziasis; and coffee-drinking. Bladder calculi and bladder papillomas may also predispose to bladder cancer. (53 refs)

78-6568 **Cancer in Cameroon: A Relative Frequency Study.** (Eng) Jensen, O. M. (Unit Epidemiology and Biostatistics, International Agency Res. Cancer, 150 Cours Albert-Thomas, 69008 Lyon, France); Tuyns, A. J.; Ravisse, P. *Rev Epidemiol Sante Publique* 26(2): 147-159; 1978.

Cancer was diagnosed and confirmed histologically in 1,390 males and 1,418 females in Cameroon, Africa, during 1969-1973. An attempt was made to correlate the cancer pattern with ethnic differences in the state. In both sexes, the pattern was dominated by a few tumor sites: men--skin 30%, malignant lymphomas 13%, and primary liver cancer 11%; women--skin 30%, uterine cervix 16%, and breast 10%. Ethnic differences were more apparent among men than women,

and they were correlated with neoplasms of the pharynx and buccal cavity, lung, connective tissue, and genitourinary tract. A close examination of tumor time trends showed that liver and respiratory tract tumors increased more rapidly than the total number of cancers. On the other hand, the same absolute number (a decreasing proportion) of skin cancers was recorded during each year of the study. These results suggest that the time trends reflect rapid changes in society and in medical facilities rather than actual changes in the frequencies of these tumors. For this reason, the results should be interpreted cautiously. (28 refs)

78-6569 **Sperm Basic Proteins and Cervical Carcinogenesis (2 Letters to Editor).** (Eng) Reid, B. L. (Dept. Obstetrics and Gynaecology, Univ. Sydney, Sydney, N.S.W., 2006 Australia); French, P. W.; Hagan, B. E.; Coppleson, M. *Lancet* 2(8093): 788-789; 1978.

Two hundred and three men, only 3 of whom were students, were examined in a previous study to determine the correlation between two sperm basic proteins, histone and protamine, and social class. Recasting of the data in nonparametric terms using the analysis of variance by ranks of Kruskal-Wallis showed a correlation that was even more significant than that found originally. Differences in the incidence of cervical cancer by social class are marked and are among the greatest of all differences known. It is possible that the importance of the environment as a constant correlate of social class difference may operate through a subtle direct effect on cellular nucleic acids. A poor environment may impoverish the genome. However, it is important to determine the effects of increased sexual activity, multiple partners, genital herpes, and intercourse only with men who wear condoms or have been vasectomized on cervical cancer incidence before coming to any definite conclusions concerning etiology or prophylaxis. (8 refs)

78-6570 **Cancer in Eastern Caribbean Islands.** (Eng) Rao, E. V. (Radiotherapy Dept., Public General Hosp., Kingston, Jamaica, W. Indies). *In: Prevention and Detection of Cancer. Proceedings of the Third International Symposium on Detection and Prevention of Cancer Held by the International Study Group for the Detection and Prevention of Cancer in New York, April 26 - May 1, 1976.* International Study Group for the Detection and Prevention of Cancer. (New York, NY): Vol. 2(Part 1), 2404 pp.; 2229-2240; 1978.

The incidence of cancer in the Eastern Caribbean Islands, based on data from the Eastern Caribbean Cancer and Clinical and Pathological Registries, was determined and compared with that in Africa, as 89% of the island residents are Negro. Since most of the islands did not keep cancer statistics, the data pertain mainly to Barbados, which contains more than half the total island populations. In 1971, there were 359 cases of cancer in Barbados, 221 in women and 138 in men. The most common types were in women, 76 of cervical carcinoma and 54 cases of breast cancer. were no cases of male breast cancer. In men, cancer stomach (18 cases), esophagus (12), and prostate (20) most prevalent. Skin cancer showed a high rate in both 28 cases in men and 23 in women. The tumor incidenc tern in other eastern Caribbean Islands (St. Vince Lucia, Dominica, etc.) was similar to that seen in Bar except for a high incidence of bone tumors in St. Vince hepatomas, lymphosarcomas, or leukemias, which are mon cancers in Africa, were observed among the popul of the Eastern Caribbean Islands. This may be due to ch in geography, environment, and/or social customs. (1

78-6571 **Relation of Dysplasia and Carcinoma o Uterine Cervix to Age at Onset of Sexua and Number of Coital Partners.** (Eng) Berget, A. (Jul 4, DK-2820 Gentofte, Denmark). *Dan Med Bull* 172-176; 1978.

Several risk factors in the development of dysplasia (D cervical carcinoma (CC) were investigated using subject took part in a CC screening test in a Danish county study comprised 67 women with a positive test (40 with 27 with D) and 488 controls with a negative test, all 30-55. The risk of developing D or CC increased wit creasing age at onset of sexual activity, evaluated fro age at first coitus and at first pregnancy. The risk als creased with number of sexual partners, and this risk ap after corrections for social status and age at onset of s activity were made. The lower the social status the earli onset of sexual activity and, in contrast to controls, w with CC or D had an increasing number of sexual par with decreasing social status. Thus, the risk of the two c tions increased with decreasing social status. Compared the middle stratum, the risk was almost five times high the low and four times lower in the high stratum. Age a coitus and number of sexual partners were considered practical use for identifying high-risk groups. In contras socioeconomic classification of women by their early e tion, used here, seems applicable to population screen The correlations between sexual behavior and D or CC port the theory that the lesions are caused by an infec agent. (29 refs)

78-6572 **Diet, Transit Time, Stool Weight, and Cancer in Two Scandinavian Populations.** MacLennan, R. (International Agency Res. Cancer, Cours Albert Thomas, 69372 Lyon, Cedex 2, France); en, O. M.; Mosbech, J.; Vuori, H. *Am J Clin Nutr* 3 S239-S242; 1978.

Diet, stool transit time, and stool weight were compar males, 55-64 yr of age, from urban Copenhagen, Den (CD), and rural Kuopio, Finland (KF), to investigat

ırfold differences in age-adjusted colon cancer incidence ınd in the two Scandinavian populations. Interviews and a ɔd and drink diary kept for four consecutive days showed ıt the high incidence CD subjects consumed significantly ɔre white wheat breads, total meats, pork, and beer, and s potatoes and milk. Although constipation and delay in ɔl passing were more common in CD, frequency of defecan and transit time were similar in both popultions, with ınsit time showing a bimodal distribution. Stool weight was nificantly higher in low incidence KF in autumn. Simple rrelation coefficients of transit time and stool weight with wel habits and diet components were calculated, and most rrelations were low. In the 5/84 significant relationships at did exist between various foods and transit time or stool ight, all were negative, and the maximum absolute value the coefficient was 0.28. Although the fiber hypothesis of lon cancer etiology was supported by computed fiber vals (30.9 g/day in KF versus 17.2 in CD), the corresponding orter mean transit time expected in KF was not noted.) refs)

3-6573 **Age at Menarche and Menopause of Uterine Cancer Patients.** (Eng) de Graaff, J. (Dept. Obtrics and Gynecology, Vrije Universiteit, Amsterdam, Nerlands); Stolte, L. A. *Eur J Obstet Gynecol Reprod Biol* 4): 187-193; 1978.

ıe ages at menarche and at menopause of 868 cervical and 5 endometrial cancer patients diagnosed during 1950-1955 d 1960-1965 were investigated. The mean age at menarche all the cancer patients occurred in accordance with the erature, at an earlier age during 1960-1965 (13.88 yr, cervil cancer group; 14.03 yr, endometrial cancer group) than ıring 1950-1955 (14.08 and 14.24 yr, respectively). Analysis the ages at menarche in relation to year of birth showed at there is no correlation between this factor and cervical endometrial cancer. However, menopause occurred later the endometrial cancer group (49.52 yr for 1950-1955, .86 yr for 1960-1965) than in the cervical cancer group 7.93 yr for 1950-1955, 48.27 yr for 1960-1965). Menopause, erefore, may be a constitutional factor in the development endometrial and/or cervical cancer. (19 refs)

3-6574 **A Note on the Use of Nitrate Fertilizers in a High-Risk Geographical Area for Stomach Cancer.** (Eng) Zaldivar, R. (International Res. Group Cancer pidemiology and Human Ecology, 5055 N.W. 7th St., Suite 06, Miami, FL, 33126). *Z Krebsforsch* 92(2): 215-216; 1978.

ı the 11 Chilean provinces that are at high risk for stomach ıncer (age-adjusted mortality rates/100,000 men, 1.3-84.1), the amount of nitrate fertilizers ($NaNO_3$, KNO_3) sed, expressed in tons of N, was 238,950 tons. In the four w-risk provinces (mortality rates 39.1-46.2/100,000 men), only 2,550 tons were used. The use of these fertilizers has been related to stomach cancer mortality. (6 refs)

78-6575 **Family Study of Gastric Carcinoma; With Special Reference to Histological Types.** (Eng) Lehtola, J. (Dept. Internal Medicine, Univ. Central Hosp., Oulu, Finland). *Scand J Gastroenterol Suppl* 13(50): 1-54; 1978.

The occurrence of gastric carcinoma (GC) was determined in 2,243 first-degree relatives of 341 patients (186 men and 155 women) with GC diagnosed in Uusimaa Province, Finland, during 1962-1963. Biopsy specimens of the probands were classified histologically as intestinal (139 cases), diffuse (67 cases), and undifferentiated (68 cases). In 67 cases, the type of GC could not be determined. The male/female ratio in the proband group was nearly identical to that for GC patients in the entire country (1.20 vs 1.28), but the mean age of the group was slightly lower than of other Finnish GC groups (62.6 vs 65.9 yr). The social group distribution of the patients was only slightly different from that of the entire Finnish population. The prevalence of GC among the 2,243 relatives was compared with that among 2,031 relatives of proband controls matched for sex and place and date of birth. Statistical analysis of the results revealed a relative GC risk of 1.50 in relatives of the probands vs controls ($p < 0.05$). When analyzed by cancer type, the relative risk was 1.41 for intestinal GC but 7.0 for diffuse GC ($p < 0.005$). No increased familial predispostion was noted in the probands with undifferentiated GC. When the relative with GC was the mother, the relative risks were 3.67 for the intestinal type cancer and 7.0 for the diffuse type. When several female relatives had GC, the relative risk increased to 8.0. Male cases showed little excess risk over control values. Further studies are warranted of the apparent familial clustering of diffuse GC, particularly among women. (177 refs)

78-6576 **The Incidence of Carcinoma in the Gastric Remnant after Resection for Benign Ulcer Disease.** (Eng) Ewerth, S. (Dept. Surgery, Karolinska Inst., Serafimer Hosp., Stockholm, Sweden); Bergstrand, O.; Hellers, G.; Ost, A. *Acta Chir Scand Suppl* (482): 2-5; 1978.

The incidence of cancer in the gastric remnant in 569 Swedish patients who had undergone gastric resection for benign ulcer disease during 1950-1953 was assessed. The operative technique was very consistent. There were 15 postoperative deaths. Tracing revealed that 223 patients had died, but in only 130 of these patients follow-up was adequate. Two cases with carcinoma in the gastric remnant, one found at autopsy and one radiologically verified, were found. Another patient with carcinoma of the distal esophagus and cardia was not included. Of the 253 patients who were alive when traced, 111 underwent endoscopy and biopsy. In one patient there was a severe dysplasia, but no invasive carcinomas were

found. The incidence of carcinoma in the gastric remnant found in this study was 0.8%, a value lower than that found 10-20 yr ago. The reason for this difference is not known, but it may be related to varying lengths of follow-up time or the marked overall decrease in the incidence of gastric cancer in Sweden. (16 refs)

78-6577 **The Incidence of Carcinoma of the Gallbladder and Bile Ducts in Sweden 1958 to 1972.** (Eng) Broden, G. (Dept. Surgery, Karolinska Inst., Serafimer Hosp., Stockholm, Sweden); Ahlberg, J.; Bengtsson, L.; Hellers, G. *Acta Chir Scand Suppl* (482): 24-25; 1978.

The incidence of gallbladder and bile duct carcinomas in Sweden during 1958-1972 was investigated. The 5,913 reported cases were divided into three groups, each covering a 5-yr period. For each period, a mean annual incidence was calculated and related to sex and age. The absolute incidence of gallbladder and bile duct carcinomas increased during the study period. The relative incidence, however, showed a significant increase only among older patients, and especially older women. The risk of developing carcinoma of the gallbladder, which is impossible to cure, may be considered an additional indication for cholecystectomy in gallstone disease. (7 refs)

78-6578 **The Changing Incidence of Malignant Melanoma of the Skin in Sweden, 1959-1968.** (Eng) Malec, E. (Dept. Plastic Surgery, Karolinska sjukhuset, Univ. Stockholm, Stockholm, Sweden); Eklund, G. *Scand J Plast Reconstr Surg* 12(1): 19-27; 1978.

The 3,289 cases of malignant melanoma of the skin recorded in the Swedish Cancer Registry between 1959 and 1968 were analyzed with regard to sex, age, anatomical site, month of registration, and mortality. During this period, the annual incidence rate (per 100,000) rose from 2.8 to 5.2 for men from 3.3 to 6.0 for women. The percentage annual incr for all sites was 7.0% for both men and women. The dence rate was higher for women than for men, with a metric annual mean of 4.4 and 4.0/100,000, respectively. trunk was the commonest site in men, with a geometric a al mean incidence of 1.66/100,000. For women, the leg the commonest site, with a corresponding incidence ra 1.64. The highest increase occurred in women aged 30- and in men between the aged 40-64 yr. Mortality rate malignant melanoma remained fairly constant, showin annual change of -2% for men and +1% for women women, the incidence of melanoma on the legs was hi during the summer months than during the winter mo This could be a direct consequence of short-term expo to UV radiation. (51 refs)

See also:

*(Rev.): 78-6002, 78-6004, 78-6009, 78-6010, 78-6
78-6017, 78-6018, 78-6019, 78-6021, 78-6
78-6027, 78-6028, 78-6029, 78-6030, 78-6
78-6032, 78-6033, 78-6034, 78-6035, 78-6
78-6037, 78-6038, 78-6039, 78-6041, 78-6
78-6043, 78-6044, 78-6049, 78-6050, 78-6
78-6066, 78-6067, 78-6068, 78-6076, 78-6

*(Chem.): 78-6131, 78-6135, 78-6136, 78-6
78-6148, 78-6153, 78-6156, 78-6
78-6183, 78-6187, 78-6243, 78-6
78-6271, 78-6288, 78-6300, 78-6

*(Phys.): 78-6370, 78-6374, 78-6376, 78-6
78-6380.

5579 **Units of Transcription for Cytoplasmic RNA in Mouse Myeloma Cells.** (Eng) Giorno, R. (Dept. hysics and Genetics, Univ. Colorado Medical Center, ver, CO, 80262); Sauerbier, W. *Proc Natl Acad Sci USA*): 4374-4378; 1978.

light mapping was used to estimate the sizes of transcrip- units for messenger RNA's (mRNA's) in mouse MPC nyeloma cells. Cells were irradiated with varying doses JV light, incubated with ^{3}H-uridine (20-40 μCi/ml) for r in the presence of actinomycin D (0.08 μg/ml), and ested. After the mRNA was purified from the cells, ap- x 10 predominant mRNA species were resolved above a kground of polydisperse mRNA by a 7 M urea/3.5% acrylamide slab gel system. UV-inactivation rates for the duction of these major mRNA's were determined and converted to transcriptional distances in DNA base s. Target size analysis of the predominant mRNA's wed that they originated within transcription units that e at least 2 and possibly up to 14 times the size of the ure mRNA species. This may be a minimum estimate, e the target size for inhibiting mRNA production may have included promoter-distal sequences if they were not essary for processing. Precursors longer than the observed get sizes may be found by complementary DNA·RNA hy- lization. (34 refs)

6580 **Non-polyadenylated Messenger Ribonucleic Acids with Affinity for Polyadenylyl-Sepharose n Friend Murine Leukaemia Cells.** (Eng) Katinakis, P. (Dept. Biochemistry, Univ. Glasgow, Glasgow G12 8QQ, tland); Burdon, R. H. *Biochem Soc Trans* 6(4): 757-758; 8.

polyribosomal RNA fraction from Friend murine leu- nia cells that has a high affinity for polyadenylic acid ly(A)]-Sepharose was characterized. This poly(A)-binding NA, which was isolated from polyribosomes on y(A)-Sepharose, did not appear to be of ribosomal origin, ts synthesis was unaffected by an agent that blocks riboso- l RNA synthesis. The RNA was released from polyribo- nes by EDTA in a manner expected of messenger RNA RNA) and, after deproteinization, it sedimented in forma- de gradients at around 20S. Poly(A)-binding RNA ap- ared to lack poly(A) sequences longer than seven nucleo- es, as judged by its inability to bind to polyuridylic acid ly(U)]-Sepharose or by ^{3}H-poly(U) hybridization. Binding intact RNA to poly(A)-Sepharose seemed to be due to a dylate-rich region that also contained other nucleotides, ably guanylate residues. When introduced into a cell-free eat germ system, poly(A)-binding RNA stimulated the corporation of several labeled amino acids into protein, in manner linearly related to the amount of added RNA. In periments in which DNA complementary to Friend cell lyadenylated mRNA was prepared using reverse transcriptase and then used against poly(A)-binding RNA, little sequence homology was found. Thus, poly(A)-binding RNA is a discrete class of nonadenylated mRNA, and it has no direct relationship to polyadenylated mRNA. (16 refs)

78-6581 **Experimental Transplantable Tumors of the Nervous System and Their Application (Meeting Abstract).** (Eng) Mennel, H. D. (Dept. Neuropathology, Univ. Freiburg, Freiburg, W. Germany); Szymas, J. S.; Tamura, M.; Zulch, K. J.; Pakula, H. *J Neuropathol Exp Neurol* 37(5): 659; 1978. (no refs)

78-6582 **DNA Modifying Enzymes of *Agrobacterium tumefaciens*: Effect of DNA Topoisomerase, Restriction Endonuclease, and Unique DNA Endonuclease on Plasmid and Plant DNA.** (Eng) LeBon, J. M. (Dept. Biochemistry, Georgetown Univ. Medical Center, Washington, DC, 20007); Kado, C. I.; Rosenthal, L. J.; Chirikjian, J. G. *Proc Natl Acad Sci USA* 75(9): 4097-4101; 1978.

Three nucleic acid enzymes of *Agrobacterium tumefaciens*, which causes crown gall disease in dicotyledonous plants, were purified and characterized. These enzymes may play a role in the infection process by catalytically activating tumorigenic genes present in the bacterium or, alternatively, by modifying plant host DNA. The first enzyme, *Atu* DNA topoisomerase, relaxed only negatively twisted DNA. The second, *Atu* I, was a type II restriction endonuclease that generated DNA digestion patterns similar to those generated by *Eco*RII with several DNA substrates. The third activity, endonuclease A, preferentially catalyzed the conversion of superhelical DNA's to their corresponding linear forms. Polyacrylamide gel electrophoresis indicated that *Atu* DNA topoisomerase unwound plasmid pCK135 DNA (obtained from the virulent strain 1D135 of *A. tumefaciens*) and had an effect on plant DNA. *Atu* I altered both plant and plasmid DNA's, but endonuclease A only altered plasmid DNA. The mobility of plasmid and plant DNA's was also altered after treatment with combinations of these enzymes, suggesting a possible role for these enzymes in vivo. (28 refs)

78-6583 **Highly Conserved DNA of Ti Plasmids Overlaps T-DNA Maintained in Plant Tumours.** (Eng) Chilton, M. D. (Dept. Microbiology and Immunology, Univ. Washington, Seattle, WA, 98195); Drummond, M. H.; Merlo, D. J.; Sciaky, D. *Nature* 275(5676): 147-149; 1978.

An attempt was made to show that part of the tumor-inducing (Ti) plasmid maintained in tumor cells (T-DNA) is highly conserved among diverse Ti plasmids. It had been suggested that since common tumor-inducing functions are a feature of every Ti plasmid, a region of homologous DNA should

be detectable in all types. Plasmid pTi-B6-806 was mapped and the T-DNA, the region of this plasmid that is maintained in the E9 tobacco tumor, was located. DNA hybridization studies were conducted to test this region of pTi-B6-806 for homology with six representative Ti plasmids. PTi-B6-806 DNA fragments to be used as probes were isolated after preparative agarose gel electrophoresis of plasmid DNA digests and labelled by the nick translation reaction. Four of the six probes hybridized with all of the Ti plasmids examined and, therefore, they must constitute a region of DNA common to all. This region extends on the map from *Sma*I fragment 17 to *Hpa*I fragment 14, a region of 5.5 x 10^6 daltons or less. However, the results also show that a significant portion of the T-DNA of pTi-B6-806 comprises DNA sequences not common to all Ti plasmids. (26 refs)

78-6584 **Homologous DNA Sequences in Different Ti-Plasmids Are Essential for Oncogenicity.** (Eng) Depicker, A. (Laboratorium voor Genetica, Rijksuniversiteit Gent, Ledeganckstraat 35, B-9000 Ghent, Belgium); Van Montagu, M.; Schell, J. *Nature* 275(5676): 150-153; 1978.

In view of the fact that different types of Ti plasmids only have a limited degree of DNA sequence homology but produce transformed plant cells with similar phenotypes, the hypothesis that at least part of the common DNA sequences would be directly and/or indirectly involved in oncogenicity was investigated. Homology between octopine and nopaline Ti plasmids was demonstrated with the use of plasmid DNA from wild-type strains of *Agrobacterium tumefaciens* (strain ACH5 was used as an example of an octopine Ti plasmid and strains C58 and K14 were used as examples of nopaline Ti plasmids). Hybridization experiments employing labeled DNA fragments showed that a specific DNA segment is common to both octopine and nopaline Ti plasmids. At least part of this common segment is involved in the oncogenic properties of the Ti plasmids, as integration of a complete P-type plasmid pRP4 into the pTI-C58 plasmid resulted in a loss of oncogenicity. Dissociation and subsequent hybridization experiments confirmed the fact the integration of pRP4 had indeed occurred in the common DNA sequence. Genetic evidence is given that the segment overlaps with the Ti plasmid DNA found in transformed plant cells. (24 refs)

78-6585 **GC/MS Determination of Cytokinins in *Agrobacterium Tumefaciens* Cultures.** (Eng) Claeys, M. (Laboratorium voor Organische Chemie, R.U.G., Krijgslaan 271 [S4], B-9000 Ghent, Belgium); Messens, E.; Van Montagu, M.; Schell, J. *Fresenius Z Anal Chem* 290(2): 125-126; 1978.

Selected ion monitoring (SIM) was used to determine the cytokinins 6-(3-methyl-2-butenylamino)purine and 6-(4-hydroxy-3-methyl-trans-2-butenylamino)purine in oncogenic and nononcogenic *Agrobacterium tumefaciens* strains. The cytokinin levels were higher in the oncogenic strains. (4 refs)

78-6586 **Disappearance of Patulin During Alcoholic mentation of Apple Juice.** (Eng) Stinson, E (Eastern Regional Res. Center, Federal Res., Science Education Admin., U.S. Dept. Agriculture, Philadelp PA, 19118); Osman, S. F.; Huhtanen, C. N.; Bills, D. D. *Environ Microbiol* 36(4): 620-622; 1978.

Patulin (PL) is a carcinogenic mycotoxin produced by spoilage organisms, incuding *Penicillium expansum*, w infects apples. Its persistence in apple juice during ferme tion was evaluated with the use of eight commercial y and three typical American fermentation procedures. In ple juice containing 15 mg/liter added PL, the level wa duced to <50 μg/liter in all but two cases (with 2 ye 50 and 70 μg/liter were found). In all cases, however, level was reduced by $>99\%$ during alcoholic fermenta In unfermented samples, the level of added PL decline only 10% when the juice was stored for 2 wk, a time e to that required for fermentation. French ciders have rela ly high PL levels, and four factors related to harvesting fermentation procedures are given that may account for result. (17 refs)

78-6587 **Fecal Profiles of Anaerobic Microflora of L Bowel Cancer Patients and Patients with N hereditary Large Bowel Polyps.** (Eng) Mastromarino, A (Div. Nutritional Biochemistry, Naylor Dana Inst., An can Health Foundation, Valhalla, NY, 10595); Reddy, B Wynder, E. L. *Cancer Res* 38(12): 4458-4462; 1978.

Differences in fecal bacteria profiles were studied in 7 nor controls, 13 patients with colorectal carcinoma, and 7 tients with nonhereditary large bowel polyps. Fresh f specimens were processed and analyzed under anaerobic ditions for bacterial growth and 7 α-dehydroxylase (7α cholesterol dehydrogenase (CD), and βglucoronidase (activites. Definitive identification of about 50 isolated erobes was based on the Gram reaction, morphology, sp test, gas-liquid chromatography, and other biochem determinations. There were no significant differences in f anaerobic microflora or total aerobic counts, which sugg that taxonomic grouping of fecal bacteria is an inadeq measure of the relative risk of developing large bowel can Results of the enzyme studies showed that 7α-D and activities were higher in samples from colorectal carcino patients and intestinal polyp patients, compared with healthy subjects, but no difference was noted in βG acti between the three groups. It is postulated that since all subjects were on a Western diet, composition of the die a major factor in microbial βG activity. (50 refs)

78-6588 **Fiber in the Diet and Carcinoma.** (Fre) Lamb R. (Service de Gastroenterologie, Hopital E uard Herriot, F69003 Lyon, France). *Bull Cancer (Pa* 65(1): 71-72; 1978.

The proposed relationship between dietary fiber and can of the colon is discussed. Dietary fiber has been define

vegetable residue remaining after acid and alkaline hysis, but this definition is not considered adequate or pre- Dietary fat and intestinal bacteria may be linked to fiber ke as factors in carcinogenesis. (no refs)

5589 **Molecular Biology of Metabolic Disease: Defects in the Regulation of Enzymic Activity.** g) Galton, D. J. (Diabetes and Lipid Res. Lab., St. Bartomew's Hosp., W. Smithfield, London EC1A 7BE, End). *Enzyme* 23(4): 274-288; 1978.

Jacob-Monod model for regulating enzyme activity was to analyze the loss of allosteric inhibition of phosphotokinase by citrate in lipomatosis, disorder of covalent vation of triglyceride lipase in triglyceride-storage dis-, and a defect in the repression of 3-hydroxy-3-methyltryl coenzyme A reductase in a new variant of familial rcholesterolemia. The enzyme regulatory defects were pared with inborn errors of metabolism. (26 refs)

5590 **Characterization of 7α-Dehydroxylase in *Clostridium leptum*.** (Eng) Stellwag, E. J. (Medical Virginia, Virginia Commonwealth Univ., Richmond, 23298); Hylemon, P. B. *Am J Clin Nutr* 31(10): -S247; 1978.

distribution and enzymatic characterization of 7-α-dehylase (7-α-DH) were studied in whole cells of *Clostridileptum* as compared to other anaerobic intestinal bac-. 7-α-DH was assayed both quantitatively and qualiely in several species of bacteria by culturing with C)-chenodeoxycholic acid. 7-α-DH activity was cted in *C. leptum*, but not in 10 other *Bacteroides* ples. Enzyme activity was seen over a broad pH e in *C. leptum*, with an optimum at 6.5-7.5. Addi- of 0.1 mM sodium cholate to the cultures insed 7-α-DH activity six- to eight-fold during the onary and declining growth phases. 2,4-Dinitroiol (0.01, 0.1, or 1 mM), carbonylcyanide-m-chloroylhydrazine (1 mM), and dicyclohexylcarbodiimide (0.2) strongly inhibited 7-α-DH activity, whereas 2-N-hep--hydroxyquinoline-N-oxide (1 mM) did not. It is othesized that 7-α-DH is found only in a restricted popun of intestinal bacteria, regulated by primary bile acid entration; under certain conditions such as diet or dis- including colon cancer, total fecal bile acids and 7-α- activity are both noted to be high. (20 refs)

5591 **Increased Sialylation of Surface Glycopeptides of Human Trophoblast Compared with Fetal from the Same Conceptus.** (Eng) Whyte, A. (Dept. Pagy, Univ. Cambridge, Cambridge, England); Loke, Y. *Exp Med* 148(4): 1087-1092; 1978.

surface glycopeptides of human trophoblastic cells were pared with those of other fetal cells from the same em- using double-labeling methods with isotopes of L-fucose and D-glucosamine. (The human trophoblast shows some of the features commonly associated with neoplasia, including cellular proliferation and localized invasion.) A faster-eluting neuraminidase-sensitive fraction was observed upon Sephadex chromatography of the trophoblasts when D-glucosamine was used as the precursor. Labeling with fucose did not appear to result in the differences, which suggests that the glycopeptides characteristic of trophoblasts contained glucosamine-derived metabolic products, including sialic acid but excluding fucose. This increased sialylation is similar to, but not identical with, modifications observed in neoplastic cells. It is postulated that two species of glycopeptides may be involved in atypical cellular behavior: one contains sialic acid and other sugars excluding fucose and is associated with localized cellular growth and invasion, and the other contains both sialic acid and fucose and is characteristic of neoplastic cells. (14 refs)

78-6592 **Retinol Induces Density-dependent Growth Inhibition and Changes in Glycolipids and LETS.** (Eng) Patt, L. M. (Biochemical Oncology, Fred Hutchinson Cancer Res. Center, Seattle, WA, 98104); Itaya, K.; Hakomori, S. *Nature* 273(5661): 379-381; 1978.

The effect of retinol on cell growth behavior, glycolipid synthesis, and surface-exposed profile of glycoproteins in NIL and NILpy hamster fibroblasts and BALB/c 3T3 mouse cells was examined. Culturing of these cells in irradiated fetal calf serum containing retinol (20 nanomoles/ml) enhanced contact orientation and density-dependent inhibition of cell growth. Associated changes in cell-surface membrane GM_3 level, ganglioside contact response, and in large, external, transformation-sensitive protein (LETS protein) were also observed. Culturing of these cells in UV-irradiated vitamin A-free medium reduced contact orientation and density-dependent inhibition of cell growth. The ability of vitamin A compounds to prevent carcinogenesis could be related to the changes in surface membrane glycolipids and glycoproteins described. However, the glycosyltransferase levels for the synthesis of hematoside in NIL cells grown in medium supplemented with retinol did not differ significantly from those in cells grown in normal medium. Thus, the biochemical basis for the effect on glycolipid synthesis and surface-labeled glycoproteins could be a more complex matter. (17 refs)

78-6593 **Dimeric and High Molecular Weight Forms of the Large External Transformation-sensitive Protein on the Surface of Chick Embryo Fibroblasts.** (Eng) McConnell, M. R. (Dept. Pharmacology, Harvard Medical Sch., Boston, MA, 02115); Blumberg, P. M.; Rossow, P. W. *J Biol Chem* 253(20): 7522-7530; 1978.

The subunit structure of the large external transformation-sensitive (LETS) protein of chick embryo fibroblasts was examined. When cells were labeled by lactoperoxidase-catalyzed iodination and analyzed on sodium dodecyl sulfate-polyacrylamide gels in the absence of a reducing agent, no more than 1% of the ^{125}I-labeled LETS protein migrated

as a monomer (mol wt: 230,000-240,000). About 20%-23% of LETS migrated as a dimer. The remaining LETS was present as a high-mol-wt (HMW) complex retained at the top of the gel. These proportions did not appear to be an artifact resulting from disulfide bond formation induced by the lactoperoxidase labeling technique. The possibility that the LETS HMW complex was actually LETS dimer that was retained at the top of the gel by trapping was also ruled out. Pulse-labeling experiments demonstrated the conversion of LETS dimer to a HMW complex. The kinetics were biphasic, with rapid conversion of most of the LETS dimer followed by slow conversion of the remainder. The proportion of LETS present as a dimer predicted from the kinetic parameters agreed well with the experimental value determined by lactoperoxidase labeling. LETS dimer and the HMW complex were shed into the medium at similar slow rates; culture conditions seemed to have little influence on the subunit structure of LETS. The significance of the LETS subunit structure for its biological activity remains to be determined. (45 refs)

78-6594 **Calcitonin Heterogeneity in Lung Cancer and Medullary Thyroid Cancer.** (Eng) Becker, K. L. (Veterans Admin. Hosp., Washington, DC); Snider, R. H.; Silva, O. L.; Moore, C. F. *Acta Endocrinol (Kbh)* 89(1): 89-99; 1978.

To determine whether there is an appreciable difference between the immunoreactive forms (iCT) of human calcitonin in bronchogenic cancer (BGC) and medullary thyroid cancer (MTC), the immunochemical heterogeneity of this hormone was compared in patients with these neoplasms. The sera of 7 MCT patients and 15 BGC patients were analyzed by radioimmunoassay, gel filtration, and region-specific antisera. The serum of the MCT patients contained seven iCT fractions ranging in mol wt from ≥ 30,000 to 2,500. In contrast, > 80% of the BGC patients had predominantly high-mol-wt iCT fractions (≥30,000 and 14,600) in their sera. Following in vitro incubation of the BGC serum at 25 C for 24 hr, the high-mol-wt fractions were converted to a heterogeneous pattern similar to that of MCT serum. Furthermore, in vitro incubation in normal human serum of the high-mol-wt fractions from MTC serum resulted in their degradation to fractions of lower mol wt. In view of the larger amounts of high-mol-wt fractions in the BGC sera and the greater recognition of these fractions by midportion antisera than by carboxyl terminal antisera, it was possible to differentiate, preoperatively, between the hypercalcitonemia of the two patient groups by comparing the midportion of carboxyl terminal ratio of serum iCT levels. Only 1/15 BGC patients had a ratio similar to that encountered with the MTC patients. (21 refs)

78-6595 **Spontaneous Hepatomas in Mice Inbred from Ha:ICR Swiss Stock of Sex, Cedar Shaving in Bedding, and Immunization with Fetal Liver or Hepatoma Cells.** (Eng) Jacobs, B. B. (American Medical Center Cancer Res. Center and Hosp., Lakewood, CO, 80214); Dieter, D. K. *J Natl Cancer Inst* 61(6): 1531-1534; 1978.

Spontaneous tumor development was compared in Ha: Swiss mice inbred (IB) by mating brother x sister for 2 generations (designated SWJ/Jac) and noninbred (NIB) r of the same strain. A total of 350 NIB females (mean age mo) were autopsied, and the following tumors were no hepatomas (5), hemangioendotheliomas (4), lymphoid mors (75), breast tumors (15), lung tumors (104), pitui tumors (58), thyroid tumors (6), and adrenal tumors When 130 female SWJ/Jac mice (33 retired breeders an virgins) were autopsied at age 12-24 mo, tumor incide were as follows: hepatomas (9), hemangioendotheliomas lymphoid tumors (36), breast tumors (5), lung tumors and pituitary tumors (1). Tumors found in 86 SWJ/Jac m autopsied at a mean age of 21.1 mo included hepatomas hemangioendotheliomas (5), lymphoid tumors (9), and tumors (17). No other tumors were seen. The hepatom this group were often multifocal; their high incidence wa due to the presence of cedar shavings in the animals' bed Treatment of 3-mo-old inbred males with crude extrac spontaneous hepatomas or fetal liver did not protect t from hepatoma development. An interesting result of t experiment was the propensity of inbred males to dev hepatomas (62.8% of animals). (12 refs)

78-6596 **Studies on the Culture of Human Cancer C Establishment of Human Rectal Cancer Lines and Their Production of Carcinoembryonic Ant (CEA).** (Jpn) Kaneko, Y. (First Dept. Surgery, Kagosh Univ. Sch. Medicine, Kagoshima, Japan). *Igaku Ke* 48(4): 298-321; 1978.

Three rectal adenocarcinoma cell lines (CaR-1, Ca CaR-3) were derived from poorly differentiated human re adenocarcinoma specimens, and their production of carc embryonic antigen (CEA) was investigated. The cells for a monolayered sheet and attached firmly to the inner sur of culture vessels. Morphologically, they showed few tub patterns and suggested signet ring cells. Electron microsc revealed epitheliallike cells with microvilli, desmosomes terdigitations, and mucinous granules. Doubling time of three cell lines was 46, 48, and 120 hr, respectively, and t respective modal chromosome numbers were 64, 63, and Histological findings of developed tumors in nude mice, lowing serial heterologous transplantation, revealed sim patterns as those in primary tumors, ie, poorly differenti adenocarcinoma. Metastatic lymph nodes were then expl ed to nude mice, and resulting tumors were cultured in v Inoculums from these tumors did not differ from cells ta directly from the original tumor. Small amounts of CEA w demonstrated in the culture medium of lines CaR-1 CaR-2 and large amounts in line CaR-3. Synthesis of C did not change for almost 10-30 serial passages. Changing medium and adding cyclic AMP and dibutyryl cyclic A to the medium of CaR-1 and CaR-2 cells did not affect C production. Electron microscopy of the high-CEA-produ CaR-3 cells showed well-developed microvilli, glycoca and microvesicles. (87 refs)

597 **Growth and Transplantability of Clonally Related Tumorigenic Murine Cell Lines.** (Eng) ker, J. R. (Univ. Warwick, Dept. Biological Sciences, entry CV4 7AL, England). *Br J Cancer* 38(4): 513-520; 3.

in vivo and in vitro growth properties of eight cloned lines derived from a transplantable adenovirus 12-in-ed CBA mouse tumor cell line, were investigated. All es were hyperdiploid, with modal numbers of 43 to 48 omosomes. Metacentric markers were usually present in or three copies per cell. Polyploidy, assessed separately, 3%-10% in all clones. Although colony morphology dif-d markedly between clones, cells within a clone were omorphic. In vitro, clone doubling times ranged from to 45.4 hr and saturation densities from 31 to 111 x 10^4 /cm^2. In their response to the cytotoxic effects of con-avalin A at different concentrations, the clones demon-ted three modes of growth that were unrelated to their origenicity in vivo. Tumorigenicity, measured by the av ber of cells required to produce tumors in 50% of inject-ites (TD_{50}), ranged from 2.5 x 10^4 cells to 6.3 x 10^5 cells. mean latent period to palpable tumor development was o 6.8 wk, and the volume doubling of established tumors to 109.4 hr. A high correlation was noted between dou-; times in vivo and in vitro, but no correlation was onstrated between in vitro growth characteristics or e morphology and tumorigenicity in vivo. (22 refs)

598 **The Growth of the EMT6 Tumour in the Lungs of BALB C Mice Following Intravenous Inocu-n of Tumour Cells from Culture.** (Eng) Twentyman, P. Dept. Radiology, Stanford Univ. Medical Center, Stan-, CA, 94305). *Cell Tissue Kinet* 11(1): 57-68; 1978.

growth of the EMT6 tumor in the lungs of Balb C mice studied following iv inoculation of different numbers of ured tumor cells. Cell suspensions were prepared from s of lungs and the number of in vitro colony forming cells ved by plating into petri dishes. Following iv injection ^{5} cells, the population doubling time of clonogenic tumor appearing in the cell suspension was 17.2 hr until such that the total tumor cell population per set of lungs hed 10^8 cells (10-12 days). Applying correction factors hanges in ability to extract cells from the lungs into the suspension at various times and also for possible changes lating efficiency in vitro, the doubling time ranged 20 to 24 hr. After reaching a total size of 10^8 tumor cells, lation doubling time of clonogenic tumor cells in the increased. During the later stages of tumor growth a correlation was seen between total lung tumor wt and umber of clonogenic cells present. For the final 3-4 days e initial period of rapid tumor growth, it is possible ob-a hemocytometer count of tumor cells in the lung suspen-By plating out various numbers of tumor cells in vitro control lungs and lungs from treated animals, the effect rious treatments on the clonogenic capacity of cells from oscopic tumor foci can be determined. (16 refs)

78-6599 **Long-Term Organ Culture of Human Uterine Endocervix.** (Eng) Schurch, W. (Dept. Pathology, Univ. Maryland Sch. Medicine, Baltimore, MD, 21201); McDowell, E. M.; Trump, B. F. *Cancer Res* 38(11, part 1): 3723-3733; 1978.

A method for maintaining explants of human uterine endocervix in organ culture for 24 wk is described. The explants were obtained from 18 patients who had hysterectomies for various uterine diseases (usually myoma) and from 2 autopsies. Explants were cultured at 36.5 C according to a long-term organ culture technique using CMRL-1066 medium. The epithelium was viable for the entire time of culture, as demonstrated by ultrastructural morphology and mitotic activity. The morphology of the epithelium was near normal for 2-4 wk. In the following weeks, a slow transformation of the columnar epithelium into a metaplastic epithelium was observed, with a loss of mucus-secreting columnar cells and ciliated cells, and the appearance of layers of cuboidal and flattened epidermoid cells was observed deep in the clefts even after 24 wk in culture. Metaplasia began at the top of the papillae and ridges and extended downward into the clefts. However, in a few areas deep in the clefts, columnar cells retained evidence of mucus secretion during the duration of culture. Transformation of columnar mucous cells into cuboidal and flattened cells with epidermoid characteristics signified the development of epidermoid metaplasia. This observation was supported by ultrastructural studies, which showed mucus secretion and early keratinization in the metaplastic cells. Mitotic figures were seen under the transmission electron microscope for up to 24 wk, and all dividing cells contained mucous granules. Long-term culture of the human endocervix may represent a useful in vitro system for testing metabolic and morphological responses to potential chemical and biological carcinogens. (29 refs)

78-6600 **In Vitro Culture of Human Leukemia Cells.** (Eng) Dicke, K. A. (Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner, Houston, TX, 77030); Spitzer, G.; Verma, D. S.; McCredie, K. B. *In: Advances in Comparative Leukemia Research 1977. Proceedings of the VIIIth International Symposium on Comparative Research on Leukemia and Related Diseases, held in Amsterdam, The Netherlands on 22-26 August, 1977.* Bentvelzen, P.; Hilgers, J.; Yohn, D. S., eds. (New York: Elsevier/North Holland Biomedical Press): 503 pp.; 311-313; 1978.

A technique was developed for the selective in vitro growth of colonies of leukemia cells. It consists of a liquid phase of 15 hr, during which phytohemagglutinin (PHA) is used as a stimulus, before a semisolid phase of 7 days. The PHA colony-formation assay was applied to cells from patients with chronic and acute myeloid leukemia, and the results were found to correlate with clinical outcome of disease in the former and tendency to early relapse in the latter. (5 refs)

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ABBREVIATIONS used in abstracts:

A	angstrom(s)
ACTH	adrenocorticotropic hormone
ADP	adenosine diphosphate
AMP	adenosine monophosphate
ATP	adenosine triphosphate
approx	approximately
av	average
BCG	bacillus Calmette-Guerin
bid	twice daily
C	degree(s) centigrade
cal	calorie(s)
kcal	kilocalorie(s)
cc	cubic centimeter(s)
Ci	curie(s)
mCi	millicurie(s)
μCi	microcurie(s)
cm	centimeter(s)
CNS	central nervous system
cpm	counts per minute
DNA	deoxyribonucleic acid
ED_{50}	median effective dose
EDTA	ethylenediamine tetraacetic acid
g	gram(s)
kg	kilogram(s)
mg	milligram(s)
μg	microgram(s)
Hb	hemoglobin
hr	hour(s)
ia	intra-arterial
id	intradermal
IgA	Immunoglobulin A
IgB	Immunoglobulin B
IgG	Immunoglobulin G
IgM	Immunoglobulin M
ILS	increased life span
im	intramuscular
ip	intraperitoneal
IU	International Unit(s)
iv	intravenous
K_m	Michaelis constant
LD	lethal dose
LD_{50}	median lethal dose
M	molar
μM	micromolar
mOsm	milliosmolar
max	maximum
mEq	milliequivalent(s)
min	minute(s)
ml	milliliter(s)
μl	microliter(s)
mm	millimeter(s)
mo	month(s)
mol wt	molecular weight
N	normal concentration
NAD	nicotinamide adenine dinucleotide
NADH	reduced nicotinamide adenine dinucleotide
NADP	nicotinamide adenine dinucleotidephosphate
NADPH	reduced nicotinamide adenine dinucleotidephosphate
NCI	National Cancer Institute
NIH	National Institutes of Health
PAS	periodic acid-Schiff
po	orally
ppb	parts per billion
ppm	parts per million
qid	four times daily
qod	every other day
QO_2	oxygen quotient
R	roentgen
RBC	red blood cells (erythrocytes)
RNA	ribonucleic acid
rpm	revolutions per minute
sc	subcutaneous
sec	second(s)
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
soln	solution
TCD	tissue culture dose
TCD_{50}	median tissue culture dose
tid	three times daily
UV	ultraviolet
WBC	white blood cells (leukocytes)
wk	week(s)
wt	weight
X	times
yr	year(s)

Withdrawn from the Library

601 **Screening Techniques for Identification of Carcinogens: An Overview.** (Eng) Magee, P. N. Res. Inst., Temple Univ. Sch. Medicine, Philadelphia, 19140). *In: Prevention and Detection of Cancer. Proceed- of the Third International Symposium on Detection and ention of Cancer Held by the International Study Group he Detection and Prevention of Cancer in New York, April May 1, 1976.* International Study Group for the Detec- and Prevention of Cancer. (New York, NY): Vol. 2(part 404 pp.; 1935-1942; 1978.

ough none of the current screening techniques for identi- chemical carcinogens are sufficiently far developed to ce conventional long-term animal studies, several show ise. Among the screening procedures reviewed are those carcinogenesis, precarcinogenesis, in vitro transforma- or mutagenesis as end points and those that depend on pecific indirect effects of carcinogens. (36 refs.)

502 **Mutation and Latency in Carcinogenesis.** (Eng) Knudson, A. G. (Inst. Cancer Res., 7701 Bur- e Ave., Philadelphia, PA, 19111). *In: Neoplastic Trans- ation: Mechanisms and Consequences. Proceedings of a ing held by the Dahlem Workshop on Neoplastic Trans- ation: Mechanisms and Consequences in Berlin, May 1977.* Dahlem Workshop on Neoplastic Transforma- Mechanisms and Consequences (Berlin, W. Germany): p.; 55-68; 1977.

nt evidence relating somatic mutation and the phenome- f latency to the origin of cancer is reviewed. A signifi- raction of human cancer seems to involve somatic muta- The chromosomal abnormalities observed in most rs may in some instances represent this mutation, but st cases these abnormalities are probably the result rath- n the cause. Many environmental carcinogens increase ontaneous mutation rates that give rise to background r incidence. Some genetic disorders predispose an in- ual to environmentally induced carcinogenesis, and oth- eate a high probability of the occurrence of site-specific rs, even in the apparent absence of environmental car- ens. The infrequent occurrence of neoplastic transfor- n of cells in the latter individuals suggests that another is required. So also do the phenomena of latency and ependence of cancer incidence. It is proposed that a car- en produces a first mutation in some cells, one of which acquires a second mutation, which might be spontane- r induced. When the first mutation is inherited, as in ominantly inherited predispositions, an environmental nogen would be expected to supply the second mutation. s case, the latent period between exposure and clinically apparent tumor should be reduced. The most satisfactory explanation for the age-dependence phenomenon is that the target cells for transformation are embryonal cells that differentiate and cease dividing. Any cancer mutations that occur after differentiation cannot be expressed. The age-specific incidence curves observed for the hereditary forms of these tumors directly reflect the median elapsed time for the occurrence of a second mutation, since the first mutation is present at the time of fertilization. This time is thus similar to the latent period observed following acute exposure to a carcinogen. (40 refs.)

78-6603 **Hormonal Control of Tumor Growth.** (Eng) Jensen, E. V. (Ben May Lab. Cancer Res., Univ. Chicago, Chicago, IL, 60637). *In: Neoplastic Transformation: Mechanisms and Consequences. Proceedings of a meeting held by the Dahlem Workshop on Neoplastic Transformation: Mechanisms and Consequences in Berlin, May 9-13, 1977.* Dahlem Workshop on Neoplastic Transformation: Mechanisms and Consequences (Berlin, W. Germany): 314 pp.; 209-225; 1977.

The relationship between steroid hormone receptors and the dependence of cancer of the breast and prostate gland on endocrine support is reviewed. Malignant tissues that depend on steroid hormones for their growth and function have a high level of receptor proteins with which the hormones combine to exert their biological effects. Some malignant neoplasms derived from hormone-dependent tissue retain the hormone dependence of the parent tissue, but others escape from hormonal control. Most hormone-dependent breast tumors can be distinguished from autonomous cancers by measuring their estrogen-receptor (estrophilin) levels. Because not all receptor-containing breast cancers are hormone-dependent, it appears that, in the case of neoplastic cells, the coupling between the synthesis of receptor protein and the need for hormonal stimulation in the nucleus is not as precise as it appears to be in normal tissues. Estrophilin levels can predict hormone dependence correctly in 85%-90% of breast cancer patients, but the fundamental criterion of hormone dependence appears to reside in the nucleus, where a simple test for susceptibility of the RNA polymerase system to stimulation by an estrogen-receptor complex might provide a more precise identification of responsive and nonresponsive cancers. Use of the progesterone receptor as a marker for the functionality of estrogen receptor in cancer cells is being evaluated. (33 refs.)

78-6604 **Overview, Fact, Myth and Speculation.** (Eng) Clayson, D. B. (Eppley Cancer Inst., Univ. Ne-

braska Medical Center, Omaha, NB, 68105). *J Environ Pathol Toxicol* 2(1): 1-8; 1978.

The validity of several assumptions regarding agents that may be considered carcinogenic to humans is questioned. All but 3 of the 20-50 agents known to be effective carcinogens in humans are also carcinogenic in animals. This indicates that between 6%-15% of transspecies extrapolations from humans to animals are discordant. The alternative approach, from the 1,000-1,500 known animal carcinogens to the human situation, is not possible because significant human exposure to many of these carcinogens may not have occurred or because epidemiologic studies may not have been performed. A new definition that would distinguish a true carcinogen from an agent that modifies the expression of another carcinogen is needed. Many of the methods for distinguishing between true carcinogens and modifiers already exist, such as microbial and mammalian cell mutation assays. Problems also exist in extrapolating from high doses, represented by the maximum tolerated dose administrated to animals, to the low doses to which humans are exposed. The current view that there is no threshold dose for a carcinogen may also require modification. As more is learned about the mechanism of carcinogenesis, it may be possible to define certain critical rate-limiting steps in the process and to understand more clearly the likely shape of the dose-response curve at levels too low to follow economically by animal bioassay. (20 refs.)

78-6605 **Problems of Assessing the Genetic Impact of Mutagens on Man (Meeting Abstract).** (Eng) Newcombe, H. B. (Biology and Health Physics Div., Atomic Energy of Canada Ltd., Chalk River, Ontario, Canada). *Can J Genet Cytol* 20(3): 451; 1978. (no refs.)

78-6606 **In Vitro Assay for Tumor Promoters and Anti-promoters.** (Eng) Chang, C. C. (Dept. Human Development, Coll. Human Medicine, Michigan State Univ., E. Lansing, MI, 48824); Trosko, J. E.; Warren, S. T. *J Environ Pathol Toxicol* 2(1): 43-64; 1978.

The literature relating to the two-stage theory of carcinogenesis is reviewed, and an in vitro assay for tumor promoters and anti-tumor promoters is described. The two-stage theory postulates that carcinogenesis requires an initiation step and a promotion step. It has also been postulated that mutagenesis is responsible for promotion. The two-stage phenomenon has been demonstrated in several in vitro systems designed to measure transformation and mutagenesis in carcinogen-exposed cells that were posttreated with tumor promoters. Tumor promoters and anti-tumor promoters modify the induction of ornithine decarboxylase, the production of plasminogen activator, and the recovery of induced mutations. The recovery of mutagen-induced ouabain-resistant mutations in cultured Chinese hamster cells was increased by treatment with 12-O-tetradecanoylphorbol-13-acetat (TPA), a tumor-promoter, and decreased by treatment wit caffeine, an anti-tumor promoter. This suggests that man induced mutations can be repressed or derepressed by pr moters or antipromoters. TPA also increased the recovery UV-induced 6-thioguanine-resistant mutants. The resul support the hypothesis that tumor initiation is due to a mut genic event, but tumor promotion is the result of an epigene ic process involving cyclic nucleotide modulation of ge expression. (95 refs)

78-6607 **Microsomal Enzyme Systems and Drug Toxici ies.** (Eng) Gillette, J. R. (Chemical Pharmacol gy Lab., Natl. Heart, Lung and Blood Inst., Bethesda, MD 20014). *In: Rat Hepatic Neoplasia: Workshop on Rat Liv Neoplasia held by William F. Merrell, Co..in Woods Hol October, 1974.* William F. Merrell, Co. (Woods Hole, MA 288 pp.; 100-113; 1978.

Toxic compounds that are converted in the body to chemica ly reactive metabolites that combine irreversibly with ma romolecules such as DNA, RNA, protein, and glycogen a discussed. The induction of liver necrosis by halobenzen illustrates many of the ways by which the severity drug-induced tissue damage can be affected by changes in th formation or fate of chemically reactive metabolites. Brom benzene-induced liver necrosis is caused by the covalent bin ing of a metabolite of bromobenzene formed by a cytochrom P-450 enzyme. The dose of bromobenzene affects the propo tion of the dose that is bound to liver microsomes as well a the effects of phenobarbital pretreatment. The reason for th dose effect is related to the fact that liver cells have sever ways of metabolizing bromobenzene. Information about th activation of chemicals in biological systems has also derive from studies with carbon tetrachloride. Although man drugs can be converted to chemically reactive metabolit and covalently bound to microsomal protein, it is not cle to what extent the covalent binding can be used to predi the incidence of various kinds of toxicity. (45 refs)

78-6608 **Unscheduled DNA Synthesis of Human Cells a Short-term Assay for Chemical Carcinogen** (Eng) Stich, H. F. (Cancer Res. Centre, Univ. British C lumbia, Vancouver, B.C., Canada); San, R. H.; Lam, P Koropatnick, J.; Lo, L. *In: Human Risk Assessment. Proce ings of the Cold Spring Harbor Conferences on Cell Prolife tion.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Co Spring Harbor: Cold Spring Harbor Laboratory): Origins Human Cancer. Vol. 4 (Book C), 583 pp.; 1499-1512; 197

The use of unscheduled DNA synthesis of human cells as short-term assay for chemical carcinogens is explored. Th extent of DNA fragmentation and repair can be estimate accurately by several methods, but the alkaline sucrose grad ent technique and the unscheduled incorporation

H-thymidine appear to be the only ones suited for large-scale esting programs. Factors affecting DNA repair levels include hyperthermia, genetics, carcinogenic and noncarcinogenic chemicals, refractory period, and species. In tests of a ossible correlation between the carcinogenicity of a compound and its ability to trigger DNA repair synthesis, only /104 carcinogens screened were not detected by the DNA epair assay. The possibility has been raised that various cell ypes can be used as target cells. This would offer the opportunity to examine the activation potential of various tissues nd to link this property with the action of organotropic carinogens. The DNA repair bioassay has also been used to tudy the effect of two chemical carcinogens applied simulneously or in sequence. When 4-nitroquinoline-1-oxide and -methyl-N′-nitro-N-nitrosoguanidine were applied sequenally or simultaneously, typically, an additive effect was oberved at lower concentrations, an inhibitory effect at higher oncentrations. This bioassay can also be used to detect deects at various steps of the repair chain, eg, in xeroderma igmentosum cells. The DNA fragmentation and DNA reair bioassays should yield information about the validity of pplying data from animals to humans or from cultured cells o in vivo conditions. (41 refs)

8-6609 **Cancer: Somatic-Genetic Considerations.** (Eng) Burnet, F. M. (Dept. Microbiology, Univ. Melourne, 48 Monomeath Ave., Canterbury, Victoria, Australia). *Adv Cancer Res* 28: 1-29; 1978.

Current knowledge of somatic-genetic factors in the etiology f cancer is reviewed. (90 refs)

8-6610 **General Properties of Cancer: Genetic Changes Group Report.** (Eng) Harnden, D. G. (Dept. Cancer Studies, Univ. Birmingham, Birmingham B15 2TJ, ngland); Knudson, A. G.; Miller, R. W.; Brookes, P.; airns, J.; Croce, C. M.; Doerfler, W.; Fialkow, P. J.; Green, .; Magee, P. N.; Muir, C. S.; Paterson, M. C.; Rajewsky, . F.; Winnacker, E. L. *In: Neoplastic Transformation: echanisms and Consequences. Proceedings of a meeting held y the Dahlem Workshop on Neoplastic Transformation: echanisms and Consequences in Berlin, May 9-13, 1977.* ahlem Workshop on Neoplastic Transformation: Mechisms and Consequences (Berlin, W. Germany): 314 pp.; 47-268; 1977.

vidence surrounding the current genetic theories of cancer iology is reviewed. A number of agents, including environental exposures of a chemical or irradiation nature in the orkplace or elsewhere are known to cause genetic changes human genomes. Viruses have been specifically implicated s being a transmissible agent in cervical cancer, Burkitt's mphoma, nasopharyngeal cancer in the Chinese, and Hodgin's disease early in life. These possible carcinogens may not always act directly, but rather through intermediates arising from metabolic processes. A few cancers are known to be caused by germinal mutations, but these mutations may also only supply a predisposition to a cancer as in Xeroderma pigmentosum. Somatic mutations as well may be causative in some tumors. Most cancers are known to be karyotypically abnormal, but except for a small number of known markers (eg, the Philadelphia chromosome) these changes are not constant from tumor to tumor and may even occur differently within a single tumor. The valid question arises as to whether the observed chromosome abnormalities are the cause or the result of the tumor. The earliest origins of tumors are being intensely studied, and the glucose-6-phosphodiesterase marker system may be of value in this regard. If genetic changes are crucial to neoplastic change, it is important to learn whether these changes are always the same or whether a subset of the possible changes is sufficient to initiate neoplasia. Study must therefore be conducted in four areas: inherited genes that predispose to malignancy, integration of oncogenic virus genomes, specific chromosome alterations, and mutational events caused by the environment or some other yet unidentified factor. (97 refs)

78-6611 **Tumor Initiation and Promotion.** (Eng) Scribner, J. D. (Pacific Northwest Res. Foundation, Seattle, WA); Suss, R. *Int Rev Exp Pathol* 18: 137-198; 1978.

The molecular basis for the initiation and promotion of carcinogeneis is reviewed in depth. Cocarcinogenesis and the implications of the two-stage regimen for humans are also covered. (213 refs)

78-6612 **Ataxia Telangiectasia: A Genetic Disorder Predisposing to Cancer and Exhibiting Hallmarks of Abnormal DNA Repair In Vitro (Meeting Abstract).** (Eng) Paterson, M. C. (Atomic Energy of Canada Ltd., Chalk River Nuclear Labs., Chalk River, Ontario, KOJ 1JO, Canada). *Can J Genet Cytol* 20(3): 435; 1978. (10 refs)

78-6613 **Environmentally Induced DNA Damage, Its Faulty Repair, and Malignant Genetic Diseases.** (Eng) Paterson, M. C. (Biology and Health Physics Div., Chalk River Nuclear Labs., Chalk River, Ontario K0J 1J0, Canada). *In: Neoplastic Transformation: Mechanisms and Consequences. Proceedings of a meeting held by the Dahlem Workshop on Neoplastic Transformation: Mechanisms and Consequences in Berlin, May 9-13, 1977.* Dahlem Workshop on Neoplastic Transformation: Mechanisms and Consequences (Berlin, W. Germany): 314 pp.; 39-53; 1977.

The carcinogenic implications of environmentally induced DNA damage and its faulty repair are reviewed. Damage to cellular DNA by physical and chemical carcinogens is a ma-

jor factor in environmental carcinogenesis. Living organisms possess several enzymatic mechanisms for repairing this damage. In bacteria, three basic mechanisms have been identified and partially characterized: photoenzymatic repair, excision repair, and recombination repair. Similar mechanisms are also present in mammalian systems, such as human cells in culture. However, it appears that mammalian DNA damaged in vivo is not repaired completely. This is ascribed to (1) nuclear proteins masking a fraction of the damage for repair enzymes and (2) cell differentiation during development, leading to low repair abilities among certain cell types. In general, the lower the proliferative capacity of a cell type, the lower its ability to repair. In addition, damage may be repaired inaccurately, possibly by error-prone mechanisms. Thus, due to incomplete and inaccurate repair, defects may accumulate in DNA, and it is postulated that this accumulation of genetic damage plays a key role in neoplastic transformation induced by physical and chemical carcinogens. This postulate is supported by the association between defective DNA repair and cancer-proneness in humans with certain rare hereditary disorders (eg, xeroderma pigmentosum and ataxia telangiectasia). It is hypothesized that altered DNA predisposes a somatic cell to malignant transformation either by increasing the frequency of mutations and chromosomal changes or by promoting transformation by oncogenic viruses. Although this hypothesis is supported by experimental evidence, the molecular events underlying the emergence of the malignancy remain obscure. (15 refs)

78-6614 **Xeroderma Pigmentosum and the Role of DNA Repair in Oncogenesis.** (Eng) Giannelli, F. (Paediatric Res. Unit, Prince Philip Res. Labs., Guy's Hosp. Medical Sch., London, SEI 9RT, England). *Bull Cancer (Paris)* 65(3): 323-334; 1978.

Xeroderma pigmentosum (XP) is discussed, with particular reference to its role as a model for actinic carcinogenesis. The light sensitivity of 80%-90% of XP patients can be explained by defects in the excision repair mechanism for reversal of DNA damage (pyrimidine dimers). Measurement of release of supercoils in DNA and the consequent reduction in the density of nucleoids has shown that strand incisions (the first step in excision repair) do not occur at normal rates in XP cells. Restoration of normal rates of DNA repair in XP patients by cell fusion has led to the conclusion that there are at least five complementation groups of the disease (A to E), of which A, C, and D are the most numerous and among which racial differences may exist. Groups A and E are complemented rapidly, group C more slowly, and group D very slowly. Ten to twenty percent of XP patients, known as XP-variants, are not defective in dimer excision but in repair synthesis of excised DNA. XP cells in culture are sensitive to many different chemical carcinogens and mutagens, which indicates that the DNA repair systems defective in XP have broad specificity and that the factor defective in XP recognizes a number of different lesions and initiates their repair by excision. This potential for chemical carcinogenesis may help explain the presence of DNA abnormalities in cells exposed to sunlight in XP patients. XP should provide a g model for the study of human actinic carcinogenesis, beca XP and normal cells seem to differ in their response to light more quantitatively than qualitatively, and phenomena of XP can be fitted to the mutational, viral, immunologic theories of cancer etiology. (81 refs)

78-6615 **Chemical-Biological Reactions Common Teratogenesis and Mutagenesis.** (Eng) Ha son, R. D. (Dept. Pharmacology, Vanderbilt Medical Cen Nashville, TN, 37232). *Environ Health Perspect* 24: 87-1 1978.

A review of the chemical-biological interactions that are co mon to the mutagenic and teratogenic responses to to chemicals is presented. The cytotoxic agents can be grou as alkylating agents, electrophilic reactants, antimetaboli intercalating agents, amino acid antagonists, spindle poiso and additional chemicals that covalently bind to DNA. kylating agents and electrophiles react by attacking nucl philic areas of biological molecules. Antimetabolites inh pathways of purine or pyrimidine biosynthesis and format of thymidylic acid. Nucleic acid replication is inhibited incorporation of these compounds into nucleic acids as b analogs. Intercalating agents insert between base pairs DNA and interfere with transcription and replicati Amino acid antagonists inhibit protein and nucleic acid s thesis by interfering with specific amino acids required protein or nucleic acid synthesis. Specific interference w asparagine, aspartic acid, glutamine, methionine, phenyla nine, and tyrosine utilization has been reported. Spindle p sons condense with microtubular protein and interfere w formation of cellular organelles and the spindle apparat Miscellaneous cytotoxins covalently bind with DNA and hibit DNA synthesis and repair. Representative examples these classes of cytotoxic agents are given and both spec and general reactions are outlined. (115 refs.)

78-6616 **Relationship Between Mutagenesis, Carci genesis and Teratogenesis (Meeting Abstra** (Eng) Magee, P. N. (Fels Res. Inst., Dept. Pathology, Tem Univ. Sch. Medicine, Philadelphia, PA). *Mutat Res* 53 224-225; 1978. (no refs)

78-6617 **IARC Monograph Programme on the Eval tion of the Carcinogenic Risk of Chemicals Humans. Preamble.** (Eng) IARC Working Group (Ly France). *In: Some N-Nitroso Compounds. Magee, P. Chairman (International Agency for Research on Can Switzerland): IARC Monographs on the Evaluation of the C cinogenic Risk of Chemicals to Humans:* Vol. 17, 365 p 11-34; 1978.

iteria established by the International Agency for Research
Cancer/World Health Organization ad hoc working
oup for evaluating the carcinogenic risk of chemicals to
mans are presented. (77 refs)

-6618 **Mutations, Chromosome Aberrations and Cancer.** (Eng) Bishun, N. (Tissue Culture and Cytonetics Unit, Res. Dept., Marie Curie Memorial Foundaon, The Chart, Oxted, Surrey, England); Smith, N.; illiams, D. *Clin Oncol* 4(3): 251-263; 1978.

e correlation among mutagenesis, clastogenesis, and carnogenesis produced by many commonly used compounds ugs, cosmetics, pesticides, food preservatives, industrial emicals, and oral contraceptives) is summarized. The sysnatic screening of chemicals for mutagenicity and chromone-breaking activity has played a significant role in estabhing the fundamental points of the chromosome theory of rcinogenesis. Recently, studies have been undertaken to ablish correlations between the chromosome damage proced by carcinogenic chemicals and the molecular aberrans that may be involved in the induction of carcinogenesis. subtle correlation was found between the mutagenic selecities and carcinogenic potential of N-acetyl-2-aminofluoe and its metabolites. Unfortunately, almost nothing is own of the molecular effects of environmental chemicals chromosomal material. However, it does not follow that hemical that is mutagenic and produces chromosomal abrmalities is necessarily carcinogenic, although there may similarities in those interactions with DNA that lead to romosomal aberrations, mutagenicity, or carcinogenicity. us, far from finding a close correlation between mutagene- and cancer development, it can be concluded that almost y chemically reactive compound, if tested by a sufficiently de range of methods, is likely to prove mutagenic in some stems. Laboratory test procedures favored for drug safety aluation are described. (18 refs)

-6619 **DNA Damage and Repair In Vivo.** (Eng) Brash, D. E. (Dept. Biophysics, Ohio State Univ., lumbus, OH, 43210); Hart, R. W. *J Environ Pathol Toxicol* 1): 79-114; 1978.

idence implicating DNA damage in carcinogenesis is briefsummarized, and in vivo methods for studying DNA adcts and excision repair and strand breaks and strand-break pair are reviewed. Induction of DNA adducts by UV light, ays, and chemical carcinogens is usually monitored rough the appearance of identified products in the DNA. romatography or immunological detection are the usual ntification techniques. DNA-protein and DNA-DNA sslinks are assayed as changes in DNA extractability, mbrane filter adsorption, melting temperature, and naturation rate. Of the five steps involved in excision repair DNA adducts, base cleavage, excision, polymerization, and ligation have been studied in vitro and in vivo; incision has only been studied in vitro. Single-strand breaks in cellular DNA in situ can arise from x- or γ-radiation, nicking during excision repair of chemical carcinogens or UV light, or replication past a damaged site. Induction and repair of strand breaks have been studied in vivo by alkaline sucrose gradient sedimentation, DNA polymerase initiation sites, hydroxyapatite chromatography, and S_1 nuclease digestion. Postreplication repair has not been studied in vivo, and photoreactivation of cyclobutane-type pyrimidine dimers in vivo has not been demonstrated. (209 refs)

78-6620 **DNA Repair Pathways: In Bacteria and in Mammalian Cells (Meeting Abstract).** (Eng) Hanawalt, P. C. (Dept. Biological Sciences, Stanford Univ., Stanford, CA, 94305). *Can J Genet Cytol* 20(3): 433; 1978. (5 refs)

78-6621 **Theoretical Mechanisms for Synthesis of Carcinogen-induced Embryonic Proteins: III. The tRNA Methylases: Methylation Mechanism and Function.** (Eng) Hancock, R. L. (High River Inst. Theoretical Cancer Study, High River, Alberta, Canada); Hancock, C. D. *Med Hypotheses* 4(5): 497-515; 1978.

It is hypothesized that redundant repressed transfer RNA (tRNA) methylase genes that are active in embryonic states can be derepressed (induced) with carcinogens in adult cells. Supportive evidence, especially from molecular model building, is presented for a mechanism of tRNA methylation. In this mechanism, the adenine moiety of S-adenosyl-L-methionine base-pairs with uracil for all tRNA methylations. These methylations may be required during transcription of a tRNA molecule in order to limit the number of possible conformers that can occur before the molecule develops further. Fragments of tRNA were suitable substrates for enzymatic methylation; however, a subtle treatment such as UV irradiation destroyed the ability of intact tRNA to act as a substrate. It is believed that the tRNA fragments necessarily have little secondary or tertiary structure, which allows the base uracil of tRNA to pair with the adenine portion of S-adenosyl-L-methionine. This theory of the function for methyl groups is discussed in light of the properties of hypomethylated tRNA's. (39 refs)

78-6622 **The Role of Specific Nucleic Acid Reactions and Their Repair.** (Eng) Brookes, P. (Inst. Cancer Res., Pollards Wood Res. Station, Chalfont St. Giles, Bucks HP8 4SP, England); King, H. W.; Newbold, R.; Osborne, M. R. *In: Characterization and Treatment of Human Tumours. Proceedings of the Seventh International Symposium on the Biological Characterization of Human Tumours held in Budapest, April 13-15, 1977.* Davis, W.; Harrap, K.

R., eds. (Amsterdam: Excerpta Medica): Advances in Tumour Prevention, Detection and Characterization. Vol. 4, 332 pp.; 58-62; 1977.

The mechanisms by which methylating agents and polycyclic hydrocarbons react with DNA are reviewed. Some methylating agents (ie, N-methyl-N-nitrosourea) react with deoxyguanosine to form O^6-methyldeoxyguanosine. It was suggested that the O^6-methylguanine moieties in DNA would base-pair with thymine and lead to transition mutations. The extent of tumor formation due to N-methyl-N′-nitro-N-nitrosoguanidine correlates with the extent of O^6-methylation of guanine. In addition, tissues able to excise O^6-methylguanine from their DNA have lower tumor incidences following treatment with a carcinogen than tissues that cannot perform this function. According to studies of polycyclic hydrocarbons, an epoxide metabolite of benzo(a)pyrene (BP) and one of 7,12-dimethylbenz(a)anthracene reacts with the 2-amino group of guanine. It is not known why hydrocarbon derivatives react with amino groups that are never attacked by classical alkylating agents. Experiments with the diol epoxide and K-region epoxide of BP indicated that the diol epoxide was the more potent mutagen of the two and that it was able to induce a high frequency of mutations at nontoxic dose levels. The two examples considered suggest that cellular DNA-repair mechanisms may ultimately determine the biological consequences of DNA-carcinogen reactions. (23 refs)

78-6623 **Biochemical Aspects of Chemical Carcinogenesis.** (Eng) Gielen, J. E. (Laboratoire de Chimie Medicale et de Toxicologie, Institut de Pathologie, Universite De Liege, B4000 Sart Tilman par Liege 1, Belgium). *Bull Cancer (Paris)* 65(3): 249-254; 1978.

A brief review is presented of the carcinogenic abilities of polycyclic aromatic hydrocarbons (PAH), with particular reference to the enzymatic systems necessary to metabolize these carcinogens, the nature of the reactive metabolites, and the cellular targets of the active compounds. PAH are highly lipophilic, and must be made more polar (hydrosoluble) in order to be eliminated from the body. Numerous enzymes and enzyme systems such as the cytochrome P450 monooxygenases, epoxide hydratase, and glutathione-S-transferase have the ability not only to detoxify and eliminate these compounds but also to act as activating agents for them when the reaction product is more active than the parent compound. The activated compounds of PAH are epoxides and dihydrodiol epoxides, which are susceptible to reaction with cellular macromolecules. The relative basal activities (influenced by physiological parameters) of these enzymes determines the intracellular concentration of the carcinogens and are more important therefore than the absolute activity, which can be modified by administration of various chemicals. The compound most likely to be the ultimate carcinogen following benzo(a)pyrene exposure is 7,8-dihydrodiol-9,10-epoxide benzo(a)pyrene. For other unsubstituted PAH, electrophilic benzylic carbonium ions should most easily appear when located in the so-called bay region of the molecule. Beca permanent alteration of the cell results from the actio these carcinogens, it is postulated that nucleophilic cen of macromolecules are subject to electrophilic attack by th compounds. Although complexes between nucleosides 7,8-dihydrodiol-9,10-epoxide benzo(a)pyrene have been lated in vitro, this phenomenon has not yet been seen in v (45 refs)

78-6624 **Characteristics of Excision Repair after H Doses of UV and Chemicals to Human C (Meeting Abstract).** (Eng) Setlow, R. B. (Biology De Brookhaven Natl. Lab., Upton, NY, 11973). *Can J G Cytol* 20(3): 436; 1978. (4 refs)

78-6625 **The Importance of the Formation and Pers ance of Alkylated Bases in DNA in the C cinogenicity of N-Nitroso Compounds (Meeting Abstra** (Eng) Pegg, A. E. (Dept. Physiology, Pennsylvania S Univ. Medical Sch., Hershey, PA, 17033). *Can J Genet C* 20(3): 435-436; 1978. (3 refs)

78-6626 **Two-Stage (Initiation-Promotion) Carcinoge sis In Vivo and In Vitro.** (Eng) Chouroulinl I. (Institut de Recherches Scientifiques sur le Can C.N.R.S., BP8, F 94800, Villejuif, France); Lasne, C. *Cancer (Paris)* 65(3): 255-264; 1978.

Current progress in the in vitro and in vivo investigatio two-stage carcinogenesis is reviewed. In vivo initiation promotion is each an incomplete carcinogenic action; ne theless almost all initiators are carcinogens. The promot on the other hand, must be irritants capable of induc hyperplasia. Because the initiation stimulus is transmi from cell to cell over time, it must involve cellular gen mechanisms. Promotion, which is reversible, seems to related to stimulation of mitosis and protein synthesis. F tumor yield should be quantitatively related to the initi dose, while promoter effectiveness should dictate the sp of tumor development. Whereas these phenomena have b successfully demonstrated using mouse skin, difficulties h been encountered in other systems. A successful in v demonstration using rat fibroblasts is reported. Initia tested were 7,12-dimethylbenz(a)anthracene (DMBA) μg/ml of medium for 24 hr), benzo(a)pyrene (BaP) (1 μg medium for 6 hr), and benzo(e)pyrene (BeP) (1 μg/m medium for 6 hr). Promoters included 12-O-tetradec oyl-phorbol-13-acetate (TPA) (0.1 μg/ml of medium at e passage) and croton-oil (CrO) (0.01 μg/ml of medium at e passage). Transformation criteria included acceleration transformation of 20% of cells (by which criterion BaP BeP followed by CrO were most effective) and accelerat to mutation in injected animals (by which criterion DM

llowed by TPA was effective and BaP followed by CrO ost effective). BeP followed by CrO did not enhance car-nogenesis. These results demonstrate effective two-stage rcinogenesis in vitro, and have implications for the occur-nce of human lung cancer, where an initiation-promotion odel can be hypothesized. (50 refs)

-6627 **Benzene--Attempts to Establish a Lower Exposure Standard in the United States. A Review.** ng) Zenz, C. (2418 Root River Parkway, West Allis, WI, 227). *Scand J Work Environ Health* 4(2): 103-113; 1978.

ne cause-and-effect relationship between benzene exposure d blood abnormalities, including certain leukemias, is re-ewed. The National Institute for Occupational Safety and ealth has recommended that occupational exposure to ben-ne be controlled to < 1 ppm in air. The current standard 10 ppm. (57 refs)

-6628 **Nitrosamines in the Atmosphere.** (Ger) Lohs, K. (Sitzungsberichte der Akademie der Wissen-haften der DDR, Berlin, E. Germany); Rolle, W.; Gehlert, *Akademie der Wissenschaften* (2): 99-105; 1978.

ne formation, toxicity, and volatility of dialkylnitrosamines)AN) are reviewed. A recent study of the effect of dimethyl-trosamine in rats led to the conclusion that the formation O-6-methylguanine is more closely associated with the car-nogenic activity of DAN than alkylation of the N-7 of gua-ne, as was previously thought. Nitrosamine analysis has come much more precise since the development of the ther-oenergy analyzer. Recent work has shown that diethylni-osamine and diethylammonium nitrate can be rapidly rmed in the gas phase, from NO_2 and diethylamine, without e influence of UV light. Review of the literature indicates at 10^{-8} mole of nitrosamine/m^3 of inspired air is dangerous humans and also that industrial sources are releasing nounts of DAN that could quickly lead to dangerous levels. 2 refs)

-6629 **Mycotoxins.** (Rus) Kravchenko, L. V. (Lab. Enzymology, Inst. Nutrition, Moscow, USSR); tel'ian, V. A. *Zh Vses Khim O-Va D.I. Mendeleieva* 23(4): 0-405; 1978.

review is presented summarizing literature pertaining to e physico-chemical properties, toxicity, and carcinogenic tivity of a series of most common mycotoxins. Such myco-xins as aflatoxins, sterigmatocystin, patulin, penicillic acid, eoskyrin, and some metabolites of Alternaria have very ong carcinogenic activity. (198 refs)

78-6630 **Oncogenesis and Vitamin A.** (Rus) Pletsityi, K. D. (Lab. Nonspecific Resistance Organism Immunity, Inst. General Pathology, Pathological Physiology, Moscow, USSR). *Vopr Onkol* 24(10): 85-92; 1978.

A review is presented of the literature concerning the role of vitamin A in tumor resistance. Experimental and clinical data has proved the association between the vitamin A deficiency and the incidence of malignant tumors. Vitamin A deficiency was shown to enhance the carcinogenic effect of benzo(a)pyrene, while administration of vitamin A or its derivatives inhibited the growth of carcinogen-induced tumors. (72 refs)

78-6631 **Inorganic Carcinogens.** (Eng) Rawson, R. W. (Univ. Texas System Cancer Center, Houston, TX). *In: Prevention and Detection of Cancer. Proceedings of the Third International Symposium on Detection and Prevention of Cancer Held by the International Study Group for the Detection and Prevention of Cancer in New York, April 26 - May 1, 1976.* International Study Group for the Detection and Prevention of Cancer. (New York, NY): Vol. 2(part 1), 2404 pp.; 1893-1906; 1978.

The role of trace metals such as As, Cd, Cr, Ni, Pb, and Be, most of which are nonessential, and asbestos in the genesis and growth of various cancers is reviewed. There is evidence that the presence of an excess amount of certain nonessential elements in an organ or in the whole organism may promote the development of cancers of the lung, gastrointestinal tract, and skin. (66 refs)

78-6632 **Nasopharyngeal Carcinoma.** (Eng) Andersson-Anvret, M. (Dept. Tumor Biology, Karolinska Inst., Stockholm, Sweden); Forsby, N.; Klein, G. *Prog Exp Tumor Res* 21: 100-116; 1978.

The association between Epstein-Barr virus (EBV) and nasopharyngeal carcinoma (NPC) is reviewed. Epidemiological studies suggest that there are intrinsic, probably genetic, cofactors in the etiology of NPC. At least four antigens, or complexes of antigens, have been shown to be EBV-determined: viral capsid antigen (VCA), membrane antigen (MA), early antigens (EA), and complement-fixing soluble antigen (CF/S) and nuclear antigen (EBNA), which are probably identical. Patients with NPC have high antibody titers against VCA, MA, EA (both restricted and diffuse components), and CF/S. EBNA has been found in the epithelial cells of NPC tumors, and there is a complete correlation between the expression of EBNA and detection of EBV DNA in the cells. A comparison of the antibody reactivities indicates that anti-VCA titers are relatively stable over a lifetime, but anti-EA is the most disease-related antibody. It is usually only present in patients with an acute lymphoproliferative, EBV-induced disease. NPC patients have increased IgA antibody levels; however, the EBV-specific IgA antibodies to

VCA and the diffuse component of EA decline to nondetectable levels after treatment of the tumor. The EBV DNA found in NPC tumors is present in the epithelial cells. EBV DNA is only found in the undifferentiated form of the tumor. Different strains of EBV may exist in tumors from different geographical areas. (94 refs)

78-6633 **Carcinogenic Mode of Action of Tissue-embedded Foreign Particles.** (Ger) Brand, G. (Dept. Microbiology, Univ. Minnesota Medical Sch., Mayo Box 196, Minneapolis, MN, 55455). *Zentralbl Bakteriol (Orig B)* 166(2/3): 159-168; 1978.

Foreign bodies such as asbestos fibers, schistosoma eggs, or artificial implants are known to cause cancer. Studies of foreign body tumorigenesis in mice have revealed a specific sequence of preneoplastic events: (1) loss of macrophage phagocytic activity; (2) fibrous conversion of the foreign bodies; and (3) during the fifth to sixth month following implantation, contact between the preneoplastic cells and the foreign body surface. The size, shape, and surface properties of the foreign bodies (chemically inert glass or plastic films) were also of decisive importance to the neoplastic process. Specific antigens and indications of immunologic surveillance were not detected. These findings may facilitate the understanding not only of asbestos carcinogenesis and the cocarcinogenic role of smoking, but of the cancer phenomenon in general. (36 refs)

78-6634 **Occupational Lung Disease.** (Eng) Jones, R. N. (Tulane Medical Center, New Orleans, LA); Weill, H. *Respiratory Care* 23(10): 989-998; 1978.

Occupational lung disorders are reviewed with regard to their causative agents and the pathologic responses evoked. Dust macules (which are caused by inhaling tin, barium, iron, or coal salts), pulmonary fibrosis, hypersensitivity pneumonia, beryllium lung disease, and obstructive airway diseases are discussed. Asbestos, arsenic, chromates, nickel, radioactive inhalants, the halo bischloromethyl ether, chloromethyl methyl ether, and vinyl chloride monomer may induce respiratory tract tumors. Asbestos may also cause cancer of the larynx and carcinoma of the gastrointestinal tract, and brain tumors and hemangiosarcoma of the liver may result from exposure to vinyl chloride. The diagnosis of occupational lung disease is discussed, as is the setting and enforcement of permissible dust exposure levels. (10 refs)

78-6635 **Cancerogenesis, Teratogenesis, Mutagenesis: Correlation Between Animal Experiments and Clinical Findings.** (Ger.) Frohberg, H. (Institut fur Toxikologie, E. Merck, Frankfurter Strasse 250, 6100 Darmstadt 1, W. Germany). *Arzneim Forsch* 28(11a): 1984-2001; 1978.

Carcinogenicity data from animal tests, epidemiological s dies and clinical experience with humans, and mutagenic tests are reviewed. A good correlation among in vivo c cinogenicity test results, teratogenic effects, and mutage effects has been found for alkylating compounds and for co pounds that can be metabolized into electrophilic agents. develop a quick test for carcinogenicity, the mutagenic effe of carcinogens on several bacteria and yeasts have been stu ied. *Salmonella typhimurium* (Ames test) is considered most suitable organism for such a quick test. The false-ne tive rate ranges from 7%-25%. The highest false-negat rate came from a study in which many carcinogenic me compounds were tested. In this study, several metals th were not carcinogenic in animals, MoVI, PtII, RhI, a RuII, gave positive results. Thus, the Ames test as curren performed is not suitable for testing the carcinogenicity metals. With microsomal activation, the Ames test gave a 9 error rate when tested on known N-nitrosamines; for poly clic aromatic hydrocarbons, the error rate was only 2 Ames and coworkers have assumed that there is a quanti tive relationship between mutagenicity and carcinogenici but other workers have not confirmed this relationship. appears that only substances that can be converted to reacti electrophilic compounds show a positive correlation betwe mutagenicity and carcinogenicity. Possible reasons for a la of correlation with other compounds include extreme volat ty, lack of activating substances, and rapid reaction of t compound with metabolites present in *S. typhimurium*. (1 refs)

78-6636 **Structural Prognostication of Carcinogenici and Tumor-Enhancing Activity in Vario Chemicals.** (Eng) Van Duuren, B. L. (Lab. Organic Chem try, New York Univ. Medical Center, New York, N 10016). *In: Prevention and Detection of Cancer. Proceedin of the Third International Symposium on Detection and P vention of Cancer Held by the International Study Group the Detection and Prevention of Cancer in New York, Ap 26 - May 1, 1976.* International Study Group for the Dete tion and Prevention of Cancer. (New York, NY): Vol. 2(pa 1), 2404 pp.; 2071-2084; 1978.

Structure-activity relationships of direct-acting alkylati agents, tumor promoters, and cocarcinogens are reviewe Among the 100 alkylating agents examined were epoxid (mono-, bi- and polyfunctional), β- and γ-lactones, and variety of chloro ethers. The β-lactones are carcinogenic b the γ-lactones are not. The bifunctional epoxides exhibit ca cinogenicity more frequently than the monofunctional an logs. In monofunctional agents, the presence of a reacti adjacent functional group results in carcinogenic activit Trichloroethylene (TCE) and vinyl chloride (VC) may b metabolized via an epoxide intermediate. TCE is carcinoge ic in mice but not in rats, and VC is a known human carcin gen. Because of the wide differences in chemical structur reactivity, and physical properties of tumor promoters, coca cinogens, and tumor inhibitors, they probably exert their a

ities in several different ways. They may simply alter the te of absorption and disappearance of a carcinogen, or they ay alter its metabolic pathway. Tumor-promoting agents, rticularly the phorbol esters, are likely to interact at the ll membrane. As a result of structure-activity studies, it has come possible to assign biological activity to certain classes compounds that have not yet been tested. (41 refs)

-6637 **Nutritional Modulation of Carcinogenesis.** (Eng) Newberne, P. M. (Dept. Nutrition Food ience, Massachusetts Inst. Technology, Cambridge, MA); gers, A. E.; Gross, R. L. *In: Third International Symposi- n on the Detection and Prevention of Cancer held by the ternational Study Group for the Prevention and Detection Cancer in New York, April 26-May 1, 1976.* International udy Group for the Prevention and Detection of Cancer ew York, NY): Vol. 1(part 1): 1193 pp.; 665-691; 1977.

sed on epidemiologic studies that clearly reveal a change the incidence of some forms of cancer when populations ve from one geographic location to another and change d habits, evidence has accumulated to indicate that nutri- n is associated with resistance or susceptibility to cancer. e following positive correlations between cancer in five jor target organs and environmental risk factors have been nclusively established: (1) esophagus: heavy consumption cigarettes and alcohol; wheat bread and tea consumption; stomach: low socioeconomic status; consumption of salt- smoked, or fermented foods; decreased consumption of v vegetables; (3) colon: increased consumption of meats, urated fats, and highly refined carbohydrates with low die- y fiber and decreased vitamin A; (4) liver: decreased die- y lipotropes and increased dietary fat; consumption of tox- such as alcohol and mycotoxins and modified microsomal dases; (5) breast: higher socioeconomic status, with in- ased consumption of animal fat; obesity, or, more likely, h increased weight and height; potential increases in estro- synthesis. It is hoped that through continued study, nu- ion may soon be used as a major modifier in efforts toward prevention of cancer. (76 refs)

-6638 **Dietary Effects on Chemical Carcinogenesis in the Livers of Rats.** (Eng) Rogers, A. E. (Lab. perimental Pathology, Dept. Nutrition and Food Science, ssachusetts Inst. Technology, Cambridge, MA, 02139). *Rat Hepatic Neoplasia: Workshop on Rat Liver Neoplasia d by William F. Merrell, Co. in Woods Hole, October, 1974.* lliam F. Merrell, Co. (Woods Hole, MA): 288 pp.; -265; 1978.

e effects of different types of diets and of specific nutrients l additives on the development of chemically induced atic tumors in rats are reviewed. Natural-ingredient diets e some degree of protection against hepatic carcinogenesis, ough the mechanism by which they do so is not known. Lipotropic factors (choline, methionine, folic acid), with the possible exception of vitamin B_{12}, protect rats against the induction of hepatic tumors by a number of chemicals, and there is evidence of direct biochemical interaction between lipotropes and carcinogens. Vitamin A protects against the induction of gastrointestinal neoplasia by aflatoxin B_1 and other carcinogens, but it does not consistently affect the induction of hepatic tumors by aflatoxin. Dietary effects on the toxicity of carcinogens may or may not correlate with their effects on carcinogenicity. Dietary manipulation offers a valuable tool for exploring the mechanisms of action of chemical carcinogens. (no refs)

78-6639 **Experimentally Produced Brain Tumors (Meeting Abstract).** (Eng) Wechsler, W. (Dept. Neuropathology, Univ. Dusseldorf, Dusseldorf, W. Germany). *J Neuropathol Exp Neurol* 37(5): 575; 1978. (no refs)

78-6640 **The Thyroid, Prolactin, and Breast Cancer.** (Eng) VanderLaan, W. P. (Scripps Clinic and Res. Foundation, 10666 N. Torrey Pines Road, La Jolla, CA, 92037); Larson, B. A. *Arch Intern Med* 138(11): 1611-1612; 1978.

The role of thyroid dysfunction and prolactin secretion in the etiology of breast cancer is reviewed. Breast cancer growth in rats can be stimulated by iodine deprivation, and rat mammary gland dysplasia may be induced by thyroid-stimulating hormone (TSH) acting directly on the breast. Prolactin is influential in murine mammary tumorigenesis. In breast cancer patients, the findings of altered TSH and prolactin responses to thyrotropin-releasing hormone may be part of a general pituitary dysfunction in breast cancer. (10 refs)

78-6641 **Correcting a Bias?** (Eng) Hutchison, G. B. (Harvard Univ. Sch. Public Health, Boston, MA, 02115); Rothman, K. J. *N Engl J Med* 299(20): 1129-1130; 1978.

An attempt to compensate for the presumed greater detection of endometrial cancer among estrogen users by choosing as a comparison group women with benign gynecologic conditions only adds to the accumulating evidence that exogenous estrogens induce endometrial cancer. In other words, it too introduces a selection bias. (4 refs)

78-6642 **Menopausal Estrogens and Endometrial Cancer.** (Eng) Weiss, N. S. (Dept. Epidemiology, Univ. Washington and Fred Hutchinson Cancer Res. Center, Seattle, WA, 98195). *In: Estrogens and Cancer. Proceedings*

of a meeting held by the Colorado Regional Cancer Center in Denver, Sept. 10, 1977. Colorado Regional Cancer Center (Denver, CO): 197 pp.; 27-34; 1978.

The relationship between endometrial cancer and the menopausal use of estrogens is discussed. The incidence of endometrial cancer in the United States rose sharply soon after the rapid increase in estrogen use among American menopausal women, whereas the incidence rate in England, where noncontraceptive estrogen use has been much less common, is lower than in the United States and has not increased during the same period. Five recent studies have shown that menopausal women with endometrial cancer had a greater exposure to exogenous estrogens than did controls. The incidence in users was estimated to be 3-10 times that in nonusers. Estrogen use has also been found to predispose to endometrial hyperplasia; women with this condition have an increased risk of carcinoma. Other evidence suggesting a causative role for the menopausal use of estrogens includes: (a) conditions in which endogenous estrogen levels are elevated or are not countered by progesterone secretion that predispose to endometrial cancer, (b) the use of noncontraceptive estrogens in the treatment of gonadal agenesis and breast cancer that leads to an increased incidence of endometrial cancer, and (c) endometrial proliferation as a prominent effect of estrogenic hormones. Other evidence suggests that if low-dose, short-duration estrogen therapy is used, the increased risk of endometrial cancer will be less than the average increase found in most of the recent studies. It is suggested that case control and cohort studies should be employed together in future studies of the relationship between noncontraceptive estrogen use and the development of endometrial cancer. (34 refs)

78-6643 **Hormonal Carcinogenesis: A Novel Hypothesis for the Role of Hormones.** (Eng) Nandi, S. (Dept. Zoology, Univ. California, Berkeley, CA, 94720). *J Environ Pathol Toxicol* 2(1): 13-20; 1978.

Information related to the role of hormones in carcinogenesis is reviewed as background for a hypothesis on hormonal carcinogenesis. The hypothesis is based on the following findings: (1) hormones regulate cell division in normal cells; (2) successful neoplastic transformation requires hormonal stimulation of cells receiving a carcinogenic insult; and (3) normal cells, when present in a high ratio, inhibit the growth of neoplastic cells. According to the hypothesis, hormones are neither mutagenic nor carcinogenic. They play a dual role in carcinogenesis induced by direct-acting carcinogens, such as viruses, chemicals, and radiation. This dual role is postulated to be (1) the fixation of neoplastically transformed cells, and (2) control of the latent period for the appearance of overt tumors by regulating the growth and ultimate death of normal cells. This would alter the ratio of normal to neoplastic cells in favor of the neoplastic cells, which would, in turn, facilitate the growth of tumor cells. This hypothesis is testable in the mammary tumor system. (40 refs)

78-6644 **Use of Hormones and Human Tumorigene** (Eng) Lewison, E. F. (Johns Hopkins Ho Baltimore, MD). *In: Third International Symposium on Detection and Prevention of Cancer held by the Internatio Study Group for the Prevention and Detection of Cance New York, April 26-May 1, 1976.* International Study Gr for the Prevention and Detection of Cancer (New York, N Vol. 1(part 1): 1193 pp.; 609-616; 1977.

The relationship between the long-term use of exogenous h mones and the development of malignant and benign tum of the breast, endometrium, vagina, and liver is review Studies showing that estrogens act directly on normal bre tissue cells by promoting growth and differentiation and t there is a high level of positive estrogen receptor in the cy plasm of about one-third of all breast cancer patients sugg that estrogen is involved in the etiology of this disease. A significant is the fact that >99% of the patients are fem However, epidemiologic studies of the relationship betw breast cancer and estrogens or oral contraceptives have yie ed inconclusive results. Recent studies have shown conc sively that the prolonged use of estrogens by postmenopau women is correlated with a marked increase in the risk developing endometrial cancer. Cancer of the vagina, a re tively rare disease, has been linked to the ingestion dur pregnancy of nonsteroid estrogens, including diethylstil strol and its various analogs, by the mothers of the patie Primary liver tumors, liver adenomas, and liver hyperpla have all been shown to develop with increased incidence young women taking oral contraceptives. In determining ultimate risk of developing malignancies in all of these sit one must take into account the exact type of synthetic est gen used as well as the duration of use. (24 refs)

78-6645 **Pathologic Aspects of Tumors and Tumor-li Lesions in Women Taking Oral Contracept Hormones.** (Eng) Fechner, R. E. (Dept. Pathology, Un Virginia Sch. Medicine, Charlottesville, VA, 22903). *In: trogens and Cancer. Proceedings of a meeting held by Colorado Regional Cancer Center in Denver, Sept. 10, 19* Colorado Regional Cancer Center (Denver, CO): 197 p 111-145; 1978.

The pathology of liver, breast, and genital tract tumors a other related lesions in women taking oral contraceptives reviewed. In addition, studies on the incidences of these mors are reviewed. The largest group of tumors that appe to be associated with hormones is in the liver. Liver c adenoma is composed of hepatocytes lined by Kuppfer ce and with nuclear variation more diverse than that seen normal liver; it contains no bile ducts or ductules. Bile du do occur in focal nodular hyperplasia, and this feature is t crucial diagnostic difference between the two condition Gross and microscopic features of these conditions do n differ in hormone users from those in nonusers. Howev some evidence suggests that there may be a quantitative crease in tumor vascular changes in women taking oral co

ceptives, as compared with those in women not taking hor-nes. Hepatocellular carcinoma is also discussed. Most estigators are inclined to agree that oral contraceptives uld not be incriminated in the pathogenesis of cervical plasia on the basis of the evidence thus far available. The lometrium is the uterine tissue most frequently altered rphologically by oral contraceptives. The changes are due inly to progestin, which may produce a conspicuous cidual reaction, while the glands become atrophic (glandu--stromal dissociation). Endometrial adenocarcinoma has en illustrated in an endometrium that exhibited stro-l-glandular dissociation. The histologic appearance of en-metrial carcinomas has been unusual in two respects. One dy demonstrated an excess of secretory and clear-cell car-oma in hormone users when compared with young women h endometrial cancer who had never used oral contracep-es. The second alteration is the greater degree of eosino-ilia in the neoplastic cells of women who have received rmones. Only a small proportion of uteri removed during after oral contraceptive therapy demonstrate morphologic anges in the myometrium or the myomas harbored therein. ginal adenosis has become clinically detectable during oral ntraceptive therapy and has regressed when the hormones re discontinued. Breast tissue undergoes no histologically tinctive changes during contraceptive hormone therapy. owever, the hormones occasionally produce lobular hyper-sia with secretory activity either in normal breast or within roadenomas. (184 refs)

-6646 **Oral Contraceptives and Cancer.** (Eng) Kretzschmar, R. M. (Dept. Obstetrics and necology, Univ. Iowa, Iowa City, IA, 52240). *CA* 28(2): 8-123; 1978.

ere is no convincing evidence that oral contraceptives use cancer, but they have been associated with the occur-nce of benign liver tumors. (no refs)

-6647 **Postmenopausal Estrogens and Endometrial Cancer: A Pathologist's Overview.** (Eng) Som-rs, S. C. (Dept. Pathology, Lenox Hill Hosp., New York, Y, 10021). *In: Estrogens and Cancer. Proceedings of a meet-g held by the Colorado Regional Cancer Center in Denver, pt. 10, 1977.* Colorado Regional Cancer Center (Denver, O): 197 pp.; 43-53; 1978.

ne relationship between the use of postmenopausal estro-ns and the development of endometrial cancer is discussed. evious epidemiologic-statistical and retrospective case con-ol studies were poorly planned and failed to answer the estions of how often and how significantly perimenopausal trogen administration may contribute to the development endometrial carcinoma. Prospective cohort studies are needed to avoid the acknowledged defects of case control and retrospective studies. It is suggested that, if there is a family history of endometrial or gastrointestinal carcinoma, obesity, diabetes, hypertension, proven endometrial hyperplasia or dysplasia, or an abnormal genotype, estrogens should probably not be given, as they might exaggerate an already abnormal situation and contribute eventually to development of endometrialcarcinoma. In other women, estrogens may be prescribed without fear of endometrial carcinogenesis, provided that an initial endometrial specimen does not exhibit hyperplasia or dysplasia, that the dose is in the low (growth stimulating) rather than in the high (growth inhibitng) range, and that the estrogen is not given continuously. If estrogen is administered in a high dose, progestagen should be administered concomitantly about 1 wk in every 4. Follow-up endometrial aspiration or curette biopsies are desirable to appraise the endometrial response at intervals. (63 refs)

78-6648 **Effect of Oral Contraceptive Use on the Risk of Human Breast and Cervical Cancer.** (Eng) Stadel, B. V. (Natl. Inst. Child Health and Human Development, NIH, Bethesda, MD, 20014). *In: Estrogens and Cancer. Proceedings of a meeting held by the Colorado Regional Cancer Center in Denver, Sept. 10, 1977.* Colorado Regional Cancer Center (Denver, CO): 197 pp.; 89-102; 1978.

The epidemiology of breast and cervical cancers and the effect of oral contraceptive (OC) use on the risk of these cancers are reviewed. No overall increase in breast cancer risk for OC users has been observed in four case control studies or three cohort studies. However, only one study specifically analyzed possible interactions between OC use and previously reported breast cancer risk factors, such as age of first full-term birth and benign breast disease. This study suggests that OC use may increase breast cancer risk among certain subgroups of women and indicates the need for further study. The available data regarding the effect of OC use on the risk of cervical cancer and its precursors are confusing and inconclusive. Most of these data do not control directly for possible confounding between OC use and either age at first coitus or number of sexual partners. The use of such variables as socioeconomic status, marital status, and parity in an effort to control indirectly for possible confounding between OC use and sexual behavior may be insufficient. Separate evaluation of the effect of OC use on the risk of cervical cancer and its precursors for women with previously reported cervical cancer risk factors would be useful, since OC use might affect risk only among women exposed to a venereally transmitted carcinogen prior to OC use. Virtually all available studies of the effect of OC use on the risk of cervical cancer and its precursors have had cervical dysplasia or carcinoma in situ as their biologic endpoint. Diagnostic criteria for these lesions appear to vary widely, as do estimates of their invasive potential. The current information is insufficient to warrant the conclusion that OC use affects the risk of either breast or cervical cancer, but it does indicate a need for further studies. (34 refs)

78-6649 **Breast Cancer and Menopausal Estrogens.** (Eng) Ross, R. (Dept. Pathology, Univ. Southern California, Sch. Medicine, Los Angeles, CA, 90033); Mack, T.; Gerkins, V.; Hill, A. *In: Estrogens and Cancer. Proceedings of a meeting held by the Colorado Regional Cancer Center in Denver, Sept. 10, 1977.* Colorado Regional Cancer Center (Denver, CO): 197 pp.; 55-65; 1978.

Despite evidence implicating estrogens in mammary tumor development in animals, the role of exogenous menopausal estrogens in human breast cancer (BC) etiology remains unresolved. Of two case-control studies, the first revealed a large protective effect of hormones, but the second showed a two-fold increased risk of BC in hormone users. When the studies were combined and adjusted for age at diagnosis and menopause, estrogens were found to have no effect. In a recent study of 1,891 women using conjugated estrogens and followed for an av of 12 yr, the overall relative risk of BC was 1.3. However, women in this study who took at least 0.625 mg estrogen on other than a daily basis and followed by > 10 yr had a relative risk of 4.7. The methodology for a current case-control study designed to overcome the methodologic errors of previous studies is described. Drug histories of cases and controls matched by age, marital status, and social class are being obtained through personal interviews, medical record abstraction, and pharmacy records, and a detailed menstrual and reproductive history is also being taken. (33 refs)

78-6650 **Oral Contraceptives and Liver Tumors.** (Eng) Bloustein, P. A. (Dept. Lab. Medicine, Wesley Medical Center, Wichita, KS, 67202). *In: Estrogens and Cancer. Proceedings of a meeting held by the Colorado Regional Cancer Center in Denver, Sept. 10, 1977.* Colorado Regional Cancer Center (Denver, CO): 197 pp.; 103-110; 1978.

Reported associations between oral contraceptive use and the development of focal nodular hyperplasia, liver adenoma, and hepatocellular carcinoma are reviewed, and the effects of oral contraceptives on liver metabolism and ultrastructure are summarized. Serum transaminase activity and bromosulphalein retention increased in women who took the first estrogen- and progestagen-containing oral contraceptives in 1960, but the incidence of markedly deranged liver function has decreased as the amount of steroids has been reduced. Liver dysfunction is usually transient, suggesting that the hepatocytes can adapt. The most striking ultrastructural change observed in the hepatocytes with oral contraceptive use was an increase in the amount of smooth endoplasmic reticulum. Some evidence suggests that the development of focal nodular hyperplasia might be related to contraceptive use, although this evidence is not as compelling as it is with other hepatic lesions. In general, the former lesion occurs in women in the child-bearing years, regardless of oral contraceptive use. Vascular lesions were described in focal nodular hyperplasia prior to the introduction of birth control pills and thus cannot be ascribed to the use of these agents. However, hemorrhage within a preexisting lesion of focal nodular hyperplasia may be related to oral contraceptive use, becau only since the advent of the pill have patients with this lesi presented with significant intrahepatic hemorrhage or actu hepatic rupture. Hepatocellular adenoma was an exception ly uncommon tumor prior to the widespread use of oral co traceptives. The incidence of this lesion has increased in cent years in women taking oral contraceptives, especially those who had taken the hormone for several years. The mo severe complication is rupture of the tumor with resulti hemorrhage. There is evidence suggesting that the tumor pr duces a biologically active substance that causes diarrh Liver cell carcinoma has been reported in women using co traceptive steroids and estrogen-like drugs, but the numb of such cases in no way represents the type of increase frequency that has been seen in adenomas. (29 refs)

78-6651 **Treatment of Menopause.** (Eng) Morris, J. M (Dept. Obstetrics and Gynecology, Yale Uni Sch. Medicine, New Haven, CT, 06516). *In: Estrogens an Cancer. Proceedings of a meeting held by the Colorado R gional Cancer Center in Denver, Sept. 10, 1977.* Colorado R gional Cancer Center (Denver, CO): 197 pp. 13-26; 1978.

The risks and benefits of hormone replacement therapy du ing menopause are discussed. Although patients taking e ogenous estrogens appear to have an increased risk of dev loping endometrial and breast cancer, there is evidence th the endometrial tumors induced by exogenous estrogen a of lower-grade malignancy than their nonexogenously i duced counterparts. In post-menopausal women, estroge administration can reverse a negative calcium balance, ha bone loss, and arrest vertebral deformity and loss of heigh (19 refs)

78-6652 **Vaginal and Cervical Pathology Associated wit Prenatal Exposure to Diethylstilbestrol.** (En Robboy, S. J. (Dept. Pathology, Massachusetts Gener Hosp., Boston, MA, 02114); Prat, J.; Welch, W. R. *In: Estr gens and Cancer. Proceedings of a meeting held by the Colora do Regional Cancer Center in Denver, Sept. 10, 1977.* Colora do Regional Cancer Center (Denver, CO): 197 pp.; 153-17 1978.

Intrauterine exposure to diethylstilbestrol (DES) has bee linked to clear cell adenocarcinoma of the vagina and cervi nonneoplastic abnormalities of the lower genital tract i women (vaginal adenosis, cervical ectropion, vaginal and ce vical ridges) and, more recently, to anomalies of the epididy mis and testis in men. The pathologic findings in DES-ex posed subjects are reviewed at length. Ongoing animal studie of the mechanisms of DES are summarized, as are clinica studies of the natural history of DES-induced adenosis an the potential risks of consuming meat from DES-fed animal during pregnancy. (52 refs)

6653 **Alcohol and Cancer.** (Eng) Tuyns, A. J. (International Agency Res. Cancer, Lyons, France). *ohol Health Res World* 2(4): 20-31; 1978.

role of alcohol in the development of cancer, particularly cer of the mouth, tongue, larynx, pharynx, esophagus, r, and lung, is reviewed. Alcohol consumption has also n associated with stomach, pancreatic, and rectal cancer. ome of these cancers, the effects of drinking and smoking usually combined in an additive or even multiplicative ner. (108 refs)

6654 **Biological Autoxidation. 1. Decontrolled Iron: An Ultimate Carcinogen and Toxicant: An Hyesis.** (Eng) Kon, S. H. (Henry Dazian Dept. Chemistry, nt Sinai Hosp., New York, NY, 10029). *Med Hypotheses* : 445-471; 1978.

accumulation of endogenous hydrolyzed iron that is out e control of ferritin is hypothesized to act as an inorganic ogen. Uncontrolled ionic iron promotes autoxidation, ch crosslinks biomolecules and produces destructive ac- ed oxygen. The disease can be initiated by the transient ons of metallic catalysts of oxidation, a foreign body, a abolic insufficiency, a burst of ionizing radiation, or free cals. These events give rise to porous residual bodies con- ing limited-access spaces (LAS), which remain as a per- ent tissue imprint. The pores exclude ferritin and diges- and antiautoxidation enzymes but admit ionic iron, ch, sheltered from ferritin, forms a decontrolled-iron pa- gen (DIP). Thus, a DIP is an accumulation of endogenous rolyzed iron in LAS, an open-pore space of a porous y. The DIP uses the energy of ambient pH fluctuations rupt from the LAS, swamp the available ferritin, poison surroundings, catalyze autoxidation, and crosslink cell ponents into additional LAS carriers. There is a striking mblance between preneoplastic carcinogenesis and DIP wth and expansion.Protein denaturants and reagents, oxi- on catalysts, metabolism inhibitors, and foreign bodies n as asbestos, all initiators of carcinogenesis, are also ators of DIP growth. It is likely that carcinogenesis in- les DIP growth as a preneoplastic stage. (121 refs)

6655 **Nitrites: The Newberne Report (Letter to Editor).** (Eng) Lachance, P. A. (Dept. Food nce, Rutgers State Univ. New Jersey, New Brunswick, 08903). *Science* 202(4368): 576; 1978.

results of a Food and Drug Administration-sponsored ly of nitrites were misinterpreted. There was no solid evi- ce in that study that nitrites are carcinogens. The results not permit assigning nitrite a proximate carcinogenic , and it was stated that nitrite appears to be more a pro- er of neoplasia than an initiator. (no refs)

78-6656 **N-Nitroso-N-ethylurea.** (Eng) IARC Working Group (Lyon, France). *In: IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man: Some N-Nitroso Compounds.* (Lyon: International Agency for Research on Cancer): 17: 191-215; 1978.

Experimental evidence on the carcinogenicity of N-nitroso-N-ethylurea (NEU) is reviewed. NEU has been used in the laboratory synthesis of diazoethane and has been studied for growth promoting activity in plants, but it has never been used commercially. The compound is carcinogenic in mice, rats, Syrian golden hamsters, rabbits, opossums, pigs, and monkeys. NEU produces benign and malignant tumors, the sites of which vary with the route of administration. Prenatal exposure induces tumors of the nervous system. Treatment of *Salmonella typhimurium, Escherichia coli,* and *Drosophila melanogaster* with NEU leads to mutations, and treatment of cultured human fibroblasts with the compound results in both chromatid and chromosome aberrations. Although no human case reports or epidemiological data were available for analysis, it was concluded that NEU should be regarded as if it were carcinogenic to humans. (101 refs)

78-6657 **Is Cigarette the Wrong Scapegoat?** (Swe) Carlens, E. (Lidingo, Sweden). *Lakartidningen* 75(40): 3531-3533; 1978.

Experimental and epidemiological studies indicate that tar containing benzopyrene (BP) is a relatively weak carcinogen. Therefore, such cigarette smoke components as acrolein, formaldehyde, and hydrocyanic acid, which contribute to BP carcinogenesis by destroying the mucociliary barrier of the lungs, are equally important factors in the genesis of lung tumors. (10 refs)

78-6658 **Is Pulmonary Dysfunction the Common Denominator for the Multiple Effects of Cigarette Smoking?** (Eng) Cohen, B. H. (Dept. Epidemiology, Johns Hopkins Univ. Sch. Hygiene and Public Health, Baltimore, MD, 21205). *Lancet* 2(8098): 1024-1027; 1978.

The hypothesis that impaired pulmonary function underlies the diversity, multiplicity, and putative "nonspecificity" of the effects of cigarette smoking was assessed in a brief literature review. The differences in degree as well as type of clinical expression probably derive from the basic role of pulmonary function in mediating the action of the many different constituents of the tobacco itself against the background of various environmental exposures and intrinsic host factors. Which of the specific effects become manifest in different individuals depends on the dynamic interplay of genes, environment, and chance that determines individual vulnerability. (38 refs)

78-6659 **Organochlorine Pesticides and Liver Cancer Deaths in the United States, 1930-1972.** (Eng) Deichmann, W. B. (Res. and Teaching Center Toxicology, Coral Gables, FL, 33124); MacDonald, W. E. *Exotoxicol Environ Saf* 1(1): 89-110; 1977.

The association between the use of organochlorine pesticides, primarily chlorophenothane (DDT), aldrin, and dieldrin, in the US and liver cancer deaths between 1930 and 1972 was investigated. Intensive and prolonged occupational exposure to these pesticides has been found to result in increased accumulation of the compounds in the body fat, emaciation, hypertension, elevated serum cholesterol, impairment of neuromuscular function, carcinoma, and generalized pathologic conditions of the liver. Other studies, however, have indicated no undesirable effects or loss of working time as a result of pesticide exposure, in spite of high body burdens. The incidence of hepatic cancer has fallen from 8.8 per 100,000 in 1930 to 5.6 per 100,000 in 1972. This steady decline in total liver cancer death rates fails to support any clear-cut evidence of an increase in liver cancer deaths since the introduction of organochlorine pesticides in the US. If any of the organochlorine pesticide compounds do have carcinogenic potential, it will first be noted in persons engaged in the manufacture, formulation, and extensive use of these compounds. (51 refs)

78-6660 **Carcinogenicity of Saccharin.** (Eng) Reuber, M. D. (Chemical Carcinogenesis Program, NCI Frederick Cancer Res. Center, Frederick, MD, 21501). *Environ Health Perspect* 25: 173-200; 1978.

Published and unpublished carcinogenicity studies of saccharin are reviewed. Saccharin is carcinogenic for the urinary bladder in rats and mice, with male rats being more susceptible than females. Rats exposed as fetuses develop neoplasms more readily than rats exposed as weanlings. The lesions in the urinary bladder go through the stages of hyperplasia, hyperplastic nodules, and carcinomas. Neoplasms of the urinary bladder in rats were not caused by stones, parasites, sodium, or impurities. There is a cocarcinogenic effect between saccharin and methylnitrosourea for the urinary bladder. Chronic renal disease appears to result from low doses of saccharin, tumors of the renal pelvis and urinary bladder from higher doses. Benign and malignant neoplasms at all sites are increased significantly in mice and rats ingesting higher doses of saccharin. These neoplasms are present in the reproductive and hematopoietic systems and, to a lesser extent, in the lungs, vascular system, and squamous epithelium. Saccharin initiates skin neoplasms when its application is followed by croton oil. Three epidemiological studies reportedly show no increase in cancer of the urinary bladder following saccharin use. However, a Canadian study found an estimated 60% increase in cancer of the urinary bladder associated with the use of artificial sweeteners in men. (60 refs)

78-6661 **Viral and Cellular Contributions to Expressi of the Transformed State.** (Eng) Pollack, R. (Dept. Microbiology, State Univ. New York, Stony Broo NY, 11594). *In: Neoplastic Transformation: Mechanisms an Consequences. Proceedings of a meeting held by the Dahle Workshop on Neoplastic Transformation: Mechanisms an Consequences in Berlin, May 9-13, 1977.* Dahlem Worksho on Neoplastic Transformation: Mechanisms and Cons quences (Berlin, W. Germany): 314 pp.; 169-179; 1977.

A review is presented of cell growth control in culture an its relationship to the virally induced progression from no mal to malignant phenotype. Although present understand ing of growth control is limited by the inability to grow man normal cell types in culture, the fibroblast model (althoug quite complex) has been well studied. Diminished serum re quirement, loss of density-dependent growth, and relaxatio of the anchorage requirement for G_1 growth are importan examples of the phenotypic changes induced by various onc genic viruses; each is sufficient to trap a normal fibroblast i the G_1 phase of the cell cycle. Tumorigenicity requires a spe cific group of phenotypic changes induced by viral genes; thi tumor syndrome has been elucidated for SV40-transforme rodent fibroblasts injected into athymic nude mice: it consist of loss of cytoarchitectural order, loss of anchorage require ment, and production of plasminogen activator (these ar necessary but not sufficient causes for tumorigenicity in thi system). Although it is known that expression of the SV4 A gene is necessary for expression of the tumor syndrome future research is needed to determine which cellular mole cules the A gene product interacts with to generate this syn drome. In addition, it is necessary to delineate syndromes o transformation for nonfibroblastic cells, which account fo more than 90% of human tumors. More recently, kerato cytes, macrophages, arterial endothelial cells, capillary mura cells, and many hormone-dependent glandular cells hav been put into culture and should aid researchers in unravelin the mechanism of expression of the transformed state. (4 refs)

78-6662 **Food: A Carcinogenic Hazard?** (Eng) Kroes, R (Lab. Pathology, Natl. Inst. Public Health, P.O Box 1, Bilthoven, Netherlands). *In: Third International Sym posium on the Detection and Prevention of Cancer held by th International Study Group for the Prevention and Detectio of Cancer in New York, April 26-May 1, 1976.* International Study Group for the Prevention and Detection of Cance (New York, NY): Vol. 1(part 1): 1193 pp.; 659-664; 1977.

Information on the possible carcinogenic hazard of food is reviewed. Natural components of food that pose a carcinogenic threat include nitrate (in spinach, leeks, and purslane), fats, and proteins. Natural contaminants of food that are carcinogenic include aflatoxin, cycasin, safrole, sterigmatocystin, penicillic acid, patulin, luteoskyrin, cyclochlorotine, and pyrrolizidine alkaloids. Manmade chemicals that contami-

foods come from a wide range of sources. The food addi-
s butter yellow, ponceaux SX, and 3R, guinea green, fuch-
amaranth furfurylfuramide, and dulcin are now
slatively prohibited, based on recent findings that they
be carcinogenic. Contamination can occur from food
xaging chemicals; ie, vinyl chloride, a proven carcinogen
is now federally regulated. Various agricultural chemi-
still in use and under suspicion include dibromoethane,
omochloropropane, aramite, chlordecone, lindane,
T, aldrin, dieldrin, and nitrogen fertilizers. In addition,
ntially carcinogenic substances used for disinfection,
vth promotion, weed and insect control, and chemical
hesis reach food as a result of environmental pollution.
last source of carcinogenic contamination is from food
cessing: smoke curing introduces polycyclic aromatic hy-
carbons, nitrate and nitrite curing introduces nitrosa-
es, and processing through the use of fungi introduces
cotoxins into the diet. (25 refs)

6663 **Potential Cancer Risk in the Graphic Arts and Textiles Industries.** (Eng) Kay, K. (Environ-
tal Sciences Lab.-Dept. Community Medicine, Mount
i Sch. Medicine, City Univ. New York, Fifth Ave. &
th St., New York, NY, 10029). *In: Third International
posium on the Detection and Prevention of Cancer held
he International Study Group for the Prevention and De-
ion of Cancer in New York, April 26-May 1, 1976.* Interna-
al Study Group for the Prevention and Detection of Can-
(New York, NY): Vol. 1(part 1): 1193 pp.; 857-899; 1977.

upational environments in the graphic arts and textiles
istries were investigated through survey of numerous es-
ishments. Examination of printing and ink establishmens
ded information on a number of chemicals. Although the
ature reports no carcinogenic effects of carbon black per
igh-boiling oils used with carbon black in inks may act
luants for cancer-producing chemicals adsorbed on the
on. Chlorinated hydrocarbon solvents, petroleum hydro-
on solvents, and high volatility solvents are used widely
may contribute to carcinogenesis although convincing
of of this is lacking. Among the polymers and solventless
found in use were formaldehyde resins, halogenated
toinitiators, benzophenone, anthraquinone, and styrene,
having chemical relatives that are proven carcinogens.
-point and felt-pen inks employ pigments and dyes com-
able to those used in printing inks and incorporate alky-
glycols, allyl alcohol-styrene polymers, formalde-
e-ketone and urea-formaldehyde resins. In the textiles
istry, the following carcinogenic dyes have been reported:
ect black 38, Direct brown 95, Direct blue 6, Disperse
ow 3, Vat green 1, and Basic green 4, all containing the
chromophore, -N=N-. Among flame retardants widely
l, tris (2,3-dibromopropyl) phosphate, and three of its
mon contaminants have been shown to be mutagenic for
idine-deficient strains of *Salmonella typhimurium.* Fur-
rmore, chemical relatives of other flame retardants, name-
halogenated and organophosphorous compounds, are known carcinogens. Finally, three fluorescent whitening agents, 3-benzyl-4-methyl-7-hydroxycoumarin,disodium 4,4′-bis-(2, 4-dimethoxybenzamido)-2,2′-stilbenedisulfonate, and disodium 4,4′bis-(4,6-dianilino-s-triazin-2-yl)amino-2,2′-stilbenedisulfonate have been shown to enhance the carcinogenic potency of germicidal UV radiation in mice. (182 refs)

78-6664 **Proposal for Abatement of Polycyclic Aromatic Hydrocarbon Levels Through Standardization of Benzo(a)pyrene Level in the Air.** (Ger) Tomingas, R. (No affiliation given); Pott, F. *Lufthyg Silikoseforsch* 10: 28-50; 1978.

In view of the carcinogenic effects of benzo(a)pyrene (BP) and other polycyclic aromatic hydrocarbons, the atmospheric BP level should be reduced to 10 nanograms/m^3. However, level should be adopted on an interim basis, because it cannot be regarded as perfectly safe. (61 refs)

78-6665 **Rationale for One Double Event in Model for Radiation Carcinogenesis (Letter to Editor).** (Eng) Baum, J. W. (Safety and Environmental Protection Div., Brookhaven Natl. Lab., Upton, NY, 11973). *Health Phys* 35(4): 581-582; 1978.

The author responds to criticism of an article on the development of the multiple simultaneous event model for radiation carcinogenesis in which the critics suggest that two double events should have been considered. Two double events had been considered and rejected because of poor fits to the experimental data. A rationale for the absence of two double events is provided by considering the possibility that these events are gene alterations: two genes located near each other at the end of the chromosome may both be lost due to a terminal deletion, but there may be no similar mechanism for a second double event in the same cell or its ancestors. The critics also referred to claims for the predictive power of the model. The model was used to make predictions primarily to design experiments to test it further and improve the model. Claims were not made concerning the probability that the predictions would be validated. (2 refs)

78-6666 **Formation of Thymine Containing Dimers in Skin Exposed to Ultraviolet Radiation.** (Eng) Johnson, B. E. (Dept. Dermatology, Univ. Dundee, Dundee, Scotland). *Bull Cancer (Paris)* 65(3): 283-297; 1978.

A review is presented of the formation of thymine dimers in skin exposed to UV radiation (UVR). UVR is known to damage nuclear DNA, causing primarily pyrimidine-pyrimidine dimers. Although thymine is always a constituent of the dimer, thymine-cytosine dimers are also readily formed. Thymine dimers revert to the monomeric form after exposure to short

wavelength UVR (240 nanometers [nm]). Photoreactivation (a photoenzymatic process dependent on long wavelength UVR [320/390 nm] or even visible radiation) also repairs dimers, although it is not well documented in mammalian systems. However, excision repair (dark repair) has been demonstrated in humans. Studies with ^{3}H-thymidine labeling and fluorescent antibody binding have provided evidence that DNA is photochemically changed in vivo in skin exposed to UVR, and that this change in DNA involves the formation of thymine dimers. Estimates of the yield of these dimers vary with radiation dose and wavelength, but the documented range is 0.016-2.6% of total DNA activity. In vitro studies have indicated linear increases in dimer yields over the range 50-1,000 Joules (J)/meter^2 (m^2), and an exposure of monolayer cultures to 100 J/m^2 at 254 or 260 nm yielded a common value of approx 0.45% of total DNA activity as dimers. The most efficient dimer-forming activity appears to occur at approx 280-290 nm, with efficiency dropping off at both limits, perhaps more steeply at the upper end. Evidence concerning the persistence of dimers in vivo is conflicting, but a decrease in dimer incidence with time after irradiation appears to occur. Although thymine-containing dimers are formed in mammalian skin exposed to UVR in vivo, a relationship between this phenomenon and neoplastic transformation in skin remains to be proven. (73 refs)

78-6667 **The Controversy over the Health Effects of Radiation.** (Eng) Najarian, T. (Boston Veterans Admin. Hosp., Boston, MA). *Technol Review* 81(2): 74-82; 1978.

Nuclear workers exposed to low levels of ionizing radiation at the Portsmouth Naval Shipyard [av lifetime exposures of 2-10 Rems (Roentgen equivalent man)] and the Hanford Atomic Plant (av lifetime exposures of 1-15 Rems) are developing leukemia and/or multiple myeloma and pancreatic cancer at higher than expected rates. An excess of leukemia deaths has also been reported in men exposed to 1 Rem during a Nevada atom bomb test. The new data are either faulty or low-level radiation is much more harmful than was assumed previously. (11 refs)

78-6668 **X-Ray Dose Fractionation and Oncogenic Transformations in Cultured Mouse Embryo Cells (2 Letters to Editor).** (Eng) Peto, R. (Dept. Regius Professor Medicine, Radcliffe Infirmary, Oxford, England); Hall, E. J.; Miller, R. *Nature* 274(5674): 926; 1978.

In a previous study of the x-ray transformation of cultured cells, an inappropriate statistical technique was used to present the data, and, as a result, the accuracy of the data in some cases was overestimated considerably. In a reply, the authors agree with this criticism but they emphasize that the conclusion that split doses produce more transformations than a single exposure of the same total dose still holds. (1 ref.)

78-6669 **Molecular Biological Aspects of Oncogen Caused by RNA Tumor Viruses.** (Ger) Chan P. (Abteilung fur Molekularbiologie, J.-W.-Goethe-Uni sitat, Theodor-Stern-Kai 7, 6000 Frankfurt-Main 70, Germany); Ebener, U.; Steel, L. K.; Laube, H.; Kornhu B.; Thorbeck, R. R. *Klin Paediatr* 190(1): 9-27; 1978.

The molecular mechanisms by which RNA tumor vir (oncornaviruses) transfer their genetic information from genomic RNA (70S RNA) of the virions to cellular D which leads to neoplastic transformation, are discussed. cial attention is focused on the biochemical and serolog properties of reverse transcriptase (RT) and the role of enzyme in the life cycle of RNA tumor viruses. The rol RT in myelofibrosis is also discussed. This RT is antigenic related to the RT of certain primate RNA tumor viruses to that of human leukemia cells. The role of RT inhibi in viral oncogenesis, particularly that of partially thiol polycytidylic acid (MPC), which has a high binding affi to viral RT, is reviewed. The results of the use of MP a few leukemia patients are reported. (141 refs.)

78-6670 **The Oncogenic Potential of Viruses.** (Eng) erfler, W. (Institut fur Genetik, Abt. fur Vir gie, Universitat Koln, Weyertal 121, 5000 Cologne 41, Germany). *In: Neoplastic Transformation: Mechanisms Consequences. Proceedings of a meeting held by the Dah Workshop on Neoplastic Transformation: Mechanisms Consequences in Berlin, May 9-13, 1977.* Dahlem Works on Neoplastic Transformation: Mechanisms and Co quences (Berlin, W. Germany): 314 pp.; 87-110; 1977.

The oncogenic potential of viruses is reviewed with resp to the mechanism of malignant transformation. A variet viruses can transform cells in culture or induce tumors animals. A transformed or tumor cell can be distinguis from a normal cell, but transformed cells do not always hibit all the properties of tumor cells. In virus-transfor cells, viral DNA persists frequently in covalent linkage w cellular DNA. Viral DNA often is integrated in the for fragments. In cells transformed by adenovirus type 12 simian virus 40, the sites of integration of the viral geno appear to differ from one cell line to another. In transfor cells, specific viral functions are expressed; in the case homologous cells transformed by RNA tumor viruses, entire viral genome is transcribed, and infectious virus is p duced. Specific viral genes appear to be essential for trans mation, in that mutants lacking these genes cannot tra form. However, normal cells contain and express these similar genes without being transformed. In fact, nearly apparently normal cells carry endogenous viruses belong to the RNA tumor virus group. Several possible mechanis relating the integration of viral genomes to neoplastic tra formation are proposed: (1) fixation of the viral genome host cells; (2) specific viral gene products (under host contr are responsible for transformation; (3) integration of vi genes causes mutations; (4) chromosome aberrations a

nslocations; (5) repair mechanisms in eukaryotic cells; and "hit-and-run" mechanism. Each of these hypotheses is mpatible with experimental observations, although they y be too limited to explain the actual biologic phenomenon transformation. In different systems, transformation may caused at different levels, and different principles may be olved. (32 refs)

-6671 **Viral "Tumor Antigens": A Novel Type of Mammalian Regulator Protein.** (Eng) Weil, R. ept. Molecular Biology, Univ. Geneva, 30 quai Ernst-Ansermet, CH-1211 Geneva 4, Switzerland). *Biochim ophys Acta* 516(3): 301-388; 1978.

ie biological relevance of polyoma virus (PyV), simian virus (SV40), and the papilloma viruses is reviewed in the gener- context of cell and tumor biology. The gene products of V and SV40, ie, their virus-specific tumor (T) antigens, em to represent a novel type of mamalian regulator pron. There is a striking contrast between the broad spectrum biological effects induced by SV40 and PyV and the small e of their genome. The late region of both viruses comises two (possibly 3) genes that specify the major (VP1) and inor (VP2 and VP3) capsid proteins. The early region, exessed before onset of viral DNA replication, comprises apox 50% of the viral genome. It contains most of the inforation for lytic infection and all for abortive infection, duction of mitosis, initiation and maintenance of cell transrmation, tumor formation in animals, and, possibly, for the pression of virus-specific transplantation antigens. The exrimental evidence is compatible with the hypothesis that l the biological effects of the early region are mediated by antigens, although their mode of action is not known. Addional topics covered include new antigens (transplantation, tal, surface, and T antigens) in virus-induced tumors, transrmation of mammalian cells in vitro, cytological and olecular events of lytic and abortive infection with PyV and V40 in tissue culture cells, the nature and biological signifince of the virus-specific imprints in PyV- and SV40-transrmed cells, and virus-specific pleiotropic effector genes and eir significance for cell transformation and tumor induon. (717 refs).

8-6672 **Advances in the Viral Etiology of Leukemia and Lymphoma.** (Eng) Gallo, R. C. (Lab. Tumor ell Biology, NCI, Bethesda, MD, 20014); Meyskens, F. L. emin *Hematol* 15(4): 379-398; 1978.

he emphasis of this review is a critical examination of evience for the presence of RNA tumor virus information in uman leukemia. This evidence comprises the detection of ntracytoplasmic particles with properties of known oncoraviruses and of reverse transcriptase (RT) related to murine nd certain nonhuman primate enzymes, the rare demonstraon of oncornaviruses by electron microscopy, and demonstration of extracellular viral particles. It is not known how the viral information enters humans and if it is important for leukemia or any disease. The major difficulty in linking C-type oncornaviruses with human disease is the rarity of isolating replicating biologically active virus from human tissue. This problem is approached by reviewing conditions under which most animal isolates are obtained. Baboon endogenous virus, simian sarcoma virus (SiSV), and gibbon ape leukemia virus may be of special interest, since components related to these viruses have been reported in human leukemic tissues. However, there are also reports of (1) a transient release of virallike particles, (2) isolation of a partially characterized infectious or transforming virus, and (3) replicating infectious virus from human cells. Failure to detect SiSV-related proviral nucleic acid sequences in human leukemic tissues may be due to the facts that SiSV is integrated only in a rare cell, complete SiSV is integrated and then completely or partially excised, or infecting virus is integrated in a tissue remote from the primary phenotypic expression. Several explanations are given for the presence of intracytoplasmic particles, which have several properties similar to those of oncornaviruses, in human leukemia cells. The detection of oncornaviruslike particles, RT and specific antibody to RT on the surface of specific types of leukemic cells may lead to the development of markers for human leukemia. (103 refs)

78-6673 **The Structure and Expression of Human Herpesvirus DNAs in Productive Infection and in Transformed Cells.** (Eng) Roizman, B. (Committee on Virology, Univ. Chicago, Chicago, IL, 60637); Frenkel, N.; Kieff, E. D.; Spear, P. G. *In: Mechanisms of Carcinogenesis. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book B), 699 pp.; 1069-1111; 1977.

The structure of herpesvirus DNA and its expression during the reproductive cycle and in transformed cells are reviewed. Evidence is presented for coordinate and sequential synthesis of viral gene products, and mechanisms and requirements for this sequential synthesis are also reviewed. Several lines of evidence indicate that posttranscriptional processing of viral RNA plays a major role in the initiation of viral polypeptide synthesis. Two representatives from the β class of herpes simplex virus (HSV) proteins (thymidine kinase and VP143) and one from the γ class (a glycoprotein) are expressed in some transformed cell lines. In studies of the presence of HSV DNA and RNA in transformed cells, the entire genome was never found. The fraction of the genome retained varied from one cell line to another and in different sublines of the same line. The number of copies of the retained sequences was relatively low. Studies with Epstein-Barr virus (EBV)-infected cells indicate that the majority of restringently infected cell lines contain most and probably all of the EBV genome. The synthesis of viral DNA in restringent infection is linked to the synthesis of cell DNA. The differences between EBV and

HSV might be a consequence of differences in inherent regulation of viral gene function in HSV- and EBV-infected cells or they might be due to differences in the inherent permissiveness of the cells transformed by these viruses. Cells transformed by HSV are permissive, whereas those transformed by EBV are largely nonpermissive. Since EBV replicates only in B lymphocytes, cell factors present in the permissive host cell but lacking in the more restrictive lymphocytes could account for the difference between HSV and EBV in the retention and expression of viral genes in transformed cells. (164 refs)

78-6674 **RD-114 Virus: Characterization and Identification.** (Eng) McAllister, R. M. (Children's Hosp. Los Angeles, 4650 Sunset Blvd., Los Angeles, CA, 90027); Gardner, M. B.; Nicolson, M. O.; Gilden, R. V.; Davidson, N. *Prog Exp Tumor Res* 21: 196-215; 1978.

Studies performed to characterize and identify RD-114 virus and to determine its role in feline and human cancer are reviewed. RD-114 virus is a xenotropic, endogenous virus of domestic cats and of several closely related feline species. A relationship between RD-114 and endogenous baboon C-type viruses has led to the suggestion that under natural conditions, C-type viral genes can be transferred between remotely phylogenically related species. Electron microscopy of the high-mol-wt RNA extracted from RD-114 virus showed that it was an inverted dimer containing two monomer subunits with symmetrically placed loops. The two monomers are joined at their nonpoly(adenosine) ends. The dimer linkage and symmetrical loops seen in RD-114 viral RNA probably are a prototype for common structural features of all mammalian C-type viral RNA's. Transfection studies indicated that human rhabdomyosarcoma productively infected with RD-114 virus contained virus-specific DNA that specifies complete information for progeny virus formation. This DNA is integrated into the chromosomal DNA. RD-114 RNA was detected in most malignant feline tissues that transcribe feline leukemia virus (FeLV) RNA, but the converse was not seen. Thus, RD-114 gene expression may be a function of dividing cells and may be activated by FeLV infection. In older cats with naturally occurring cancer, however, transcription and translation of the endogenous RD-114 genome was not detected in the absence of FeLV expression. (78 refs)

78-6675 **Synthesis and Processing of the Translational Products of RNA Tumor Viruses.** (Eng) Jamjoom, G. A. (Riyadh Univ. Sch. Medicine, Riyadh, Saudi Arabia); Arlinghaus, R. B. *Methods Cancer Res* 15: 3-67; 1978.

The characterization of the translation products of some RNA tumor viruses is reviewed. The virus life cycle, the structure of the viral genome, and the identification and mapping of viral genes are discussed. The major polypeptides of the mature virions of murine and avian C-type viruses tabulated. Studies of virus-specific messenger RNA (mRN indicate that the mRNA's for the *gag* and *pol* gene prod are genome-length RNA species that appear to be ident to the viral genomic RNA. The mRNA's for the *env* and gene products include segments of the genome extend from the *env* or *src* gene, respectively, to the 3'-end. The gene product is required for cell transformation. Modi uncleaved precursors of the core proteins have been identi on the surface of mouse leukemia cells. The ability of th precursors to interact with nucleic acids and to associate v the cell membrane suggests that they may be capable of in fering with normal processes under conditions in which t accumulate in the cells. Exchange of genetic material am endogenous viruses of the murine system may play a rol the etiology of mouse leukemia. Evidence that the recon nant MCF viruses are the cause of leukemia in AKR m is suggestive but still circumstantial. Studies of the pep maps of gp70 molecules from MCF viruses and AKv viru indicate that recombination does occur and that it occur the *env* gene. There is probably more than one way in wh cells can become malignant, at least where C-type viruses concerned. Two different genes, *src* and *env*, appear to important in virus-induced sarcomas and leukemias, resp tively. The gene products are different in structure, and th mode of action may also be different. (242 refs)

78-6676 **Avian Leukemia Viruses: Interaction with Ta Target Cells In Vivo and In Vitro.** (Eng) G T. (German Cancer Res. Center, Neuenheimerfeld 2 D-6900 Heidelberg, W. Germany); Beug, H. *Biochim Biop Acta* 516(3): 269-299; 1978.

The origin, oncogenic spectrum, in vitro target cell speci ty, and genetic properties of avian leukemia viruses (AL are reviewed. Both nondefective LV, which predomina induce lymphatic leukemias after long latency periods, defective LV, which predominantly cause acute erythr and myeloid leukemias after short latency periods, are c ered. Susceptibility and resistance to avian sarcoma viru (ASV) and nondefective LV are determined by dominant lular genes and by specific properties of the lymphoid ta cells. Nongenetic factors that determine susceptibility a resistance include the host immune system, inoculation ro the way in which the virus was passaged or selected, and type of tumor cells from which the virus was obtained. oncogenic spectrum and latency period do not allow an ac rate distinction between ASV and the different types of A Since none of the ALV apparently possess the *src* gen ASV, this property is proposed as a main distinguishing cr rion. It is suggested that highly leukemogenic, defective have evolved from low leukemogenic, nondefective strain a multistep process involving the acquisition of several properties. A tentative and highly speculative model leukemogenesis by defective LV is presented. The mode based on three assumptions: the transformation gene of de tive LV represents a modified sequence of a cellular g

red for normal differentiation; a necessary step in topoietic differentiation is the interaction of an early entiation factor with a certain cellular protein, thereby ring the synthesis or activation of differentiation factors cteristic of later stages; the virus-coded transformation n is still capable of binding to the early differentiation . The most obvious explanation for the transformation cell specificity of ALV in hematopoietic cells is the ility that they are able to infect and replicate only in n types of cells. (150 refs)

77 **Oncornavirus Leukemogenesis as a Model for Selective Neoplastic Transformation.** (Eng) man, I. L. (Lab. Experimental Oncology, Dept. Pagy, Stanford Univ., Stanford, CA, 94305); Baird, S. *In: lastic Transformation: Mechanisms and Consequences. edings of a meeting held by the Dahlem Workshop on lastic Transformation: Mechanisms and Consequences in , May 9-13, 1977.* Dahlem Workshop on Neoplastic formation: Mechanisms and Consequences (Berlin, W. any): 314 pp.; 135-152; 1977.

iew is presented of the classification, pathogenetic role, nctions of oncornaviruses (ORV). ORV are subdivided wo groups on the basis of whether they carry the early late gene for the expression of the malignant phenotype get cells. Specific loci on the chromosomes of rapidly forming (RT) ORV code for malignant phenotype ssion within hours to days after host cells are infected. genome of the RT avian ORV has been defined by the ving genes: *gag* which codes for a polyprotein precursor; hich codes for nucleic acid polymerases; *env* which for a budding site polyprotein; *sarc*, the transforming "*c*" which codes for common oligonucleotides; and *poly* function unknown. Most RT ORV are replication-defecnd require the aid of a "helper virus" to produce budvirions in host cells. Some ORV are slowly transforming nd induce lymphocytic-leukemia weeks to months after lation into target host cells; helper viruses usually fall his group. These viruses do not carry the *sarc* gene and ot able to transform lymphocytes but may transform lasts. Many model systems emphasize the fact that nant transformation by ST ORV requires a specific inion between cell and virus and that replication and tranion of the viral genome is not sufficient to cause maligtransformation in cells other than susceptible thymic hocytes. Pathogenesis by ST ORV involves preleukemic eukemic phases that select for expression of virion proantigens. Various models are presented that attempt to nt for the origin, embryonic function, and leukemogenion of these viruses including the oncogene, protovirus, gene, and receptor-mediated transformation models. (24

678 **The Genome of the Mammalian Sarcoma Viruses.** (Eng) Van Zaane, D. (Dept. Virology, Central Veterinary Inst., Lelystad, Netherlands); Bloemers, H. P. *Biochim Biophys Acta* 516(3): 249-268; 1978.

Recent developments concerning the genetic functions of murine sarcoma viruses (SV) and other replication-defective (RD) mammalian C-type viruses [Abelson leukemia virus (AbLV), nonmurine mammalian SV, spleen focus-forming virus (SFFV)] are reviewed. These viruses share several characteristics: they are able to transform cells in vitro and are oncogenic in vivo; they are RD and can be rescued from nonproducer cells by helper LV, yielding pseudotype viruses; their genome, which consists of a 30S RNA subunit (approx 6,000 nucleotides), evolved by recombination of LV-specific genetic information and sequences derived from normal rat cells (Kirsten and Harvey SV), normal mouse cells (Moloney SV), or xenotropic murine LV (SFFV). The origin of the non-LV sequences in the genomes of AbLV, feline SV, and woolly monkey SV is unknown. At least one of the functions of the LV sequences in the RD viral genomes may be to provide 3'- and 5'-terminal ends necessary for circularization and integration of the defective genome in the chromosomal DNA of a susceptible host cell. Several findings are given to support this speculation. The gene products of the *gag*, *pol*, or *env* genes of the LV genome are apparently not required for cell transformation by SV because they are partly or completely absent in transformed nonproducer cells infected by different SV. This does not exclude the possibility that unexpressed *gag*, *pol*, or *env* gene sequences are present and play a role in transformation or that a putative LV-specific *onc* gene cooperates somehow with SV-specific sequences. The non-LV sequences in the genome of most RD viruses are not related to each other. Apparently, SV and other RD transforming C-type viruses are vehicles of sequences that are involved in malignant transformation and, possibly, in unknown processes in normal cells. (145 refs)

78-6679 **Search for RNA Tumor Virus in Humans.** (Eng) Gardner, M. B. (Dept. Pathology, Univ. Southern California Sch. Medicine, Los Angeles, CA, 90033); Rasheed, S.; Shimizu, S.; Rongey, R. W.; Henderson, B. E.; McAllister, R. M.; Klement, V.; Charman, H. P.; Gilden, R. V.; Heberling, R. L.; Huebner, R. J. *In: Mechanisms of Carcinogenesis. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4 (Book B), 699 pp.; 1235-1251; 1977.

A number of unsuccessful attempts to identify RNA tumor viruses in human material, using techniques that have proved successful in identifying RNA tumor viruses in animal tumor systems, are summarized. Virus particles could not be identified by electron microscopy, infectious viruses could not be isolated from cultured human tissues, and virus antigens or antibodies could not be identified by radioimmunoassay in a large number of human specimens. These specimens were tissues and sera from patients with a variety of cancers and

diseases (sarcomas, carcinomas, lymphomas, leukemias, lupus erythematosus, xeroderma pigmentosum, and others). The fact that no antibodies to the well-characterized RNA tumor viruses of animal origin were detected in the many hundreds of human sera tested (not even in sera from individuals known to have been exposed to such viruses, eg, feline leukemia virus) is strong evidence against the horizontal infection of humans with any of the known mammalian C-type viruses. These results, however, do not rule out the possibility that noninfectious endogenous RNA tumor viral genomes are present in human cells. (55 refs)

78-6680 **Limited In Vitro Replicative Lifespan of Cultured Human Epithelial Cells: A Survey of Recent Literature.** (Eng) Ruben, R. L. (Dept. Anatomy, Hahnemann Medical Coll., 230 Broad St., Philadelphia, PA, 19102). *Growth* 42(10): 357-368; 1978.

The literature concerning limits to the in vitro replicative life span of normal, neoplastic, and virus-transformed human epithelial cells is reviewed. Normal diploid cells routinely undergo protracted crisis in vitro, leading to the eventual loss of the cultures. Epithelial cell tumors, such as melanomas, oat cell carcinomas, and colorectal adenocarcinomas, have met with greater culturing success. However, all cell lines surviving long-term culture have had an aneuploid karyotype. Neoplastic and virus-transformed cells either degenerate in culture if diploid or survive the degenerative phase if aneuploid. Since most cells of autochthonous tumors in vivo are diploid, aneuploidy and immortality may be associated with primary or secondary transformation in vitro rather than with malignancy in vivo. In view of this evidence, the concept that neoplastic or virus-transformed cells possess unlimited potential for division should be reevaluated. (66 refs)

78-6681 **Patterns of Gene Expression and the Cellular Origins of Human Leukaemias.** (Eng) Greaves, M. (Membrane Immunology Lab., Imperial Cancer Res. Fund, London, England); Janossy, G. *Biochim Biophys Acta* 516(2): 193-230; 1978.

Detailed phenotypic profiles on human lymphoid leukemias and on permanent cell lines established from the leukemic cells were studied to determine whether there are any consistent antigenic properties of these leukemias and whether there are any antigens of the tumor cells that could be recognized by the host. The currently available data suggest that: (1) most, if not all, of human hematopoietic malignancies are monoclonal derivatives of cells resident at the time of leukemia initiation in various linkage and differentiation compartments from the common lymphomyeloid progenitors; (2) with improved banding techniques, a high frequency of nonrandom chromosomal alterations are detectable in leukemia; (3) leukemic cells express a relatively stable morphological, cytochemical, enzymatic, and antigenic phenotype that i probably unique for and qualitatively normal for the cell line age in which the disease arises; and (4) there is no unequivoca evidence at present for leukemia-specific membrane antigen or other alterations. These interpretations challenge the ra tionale of immunotherapy aimed at deliberate autoimmunit in leukemia and suggest that consistent and qualitativel unique membrane changes in neoplasia may not exist. (22 refs)

78-6682 **Stress and Disease: The Missing Link. A Vasos pastic Theory. III. Stress, Vasospasm and Gen eral Disease.** (Eng) Boyd, G. W. (Univ. Dept. Medicine, 4 Collins St., Hobart 7000, Australia). *Med Hypotheses* 4(5) 432-444; 1978.

Repeated ischemic cell damage from vasospasm may be factor in the development of autoimmune disease and cance DNA may be altered directly or through errors in DNA re plication. The similarities between viral transformation an neoplasia have led to the proposition that much cancer migh be explained if, as a species, humans have evolved by th gradual build-up of viruses. (66 refs)

78-6683 **Herpesviruses, Veneral Disease, and Cancer** (Eng) Rapp, F. (Dept. Microbiology, Milton S Hershey Medical Center, Pennsylvania State Univ., Hershey PA, 17033). *Am Sci* 66(6): 670-674; 1978.

The probability is significant that certain human tumors may in part, be caused by herpesviruses (HV). Epstein-Barr viru is uniformly associated with Burkitt's lymphoma, nasop pharyngeal carcinoma in the southern Chinese, and a signif cant percentage of non-African lymphomas. Herpes simple virus type 2, which causes venereal diseases, is associate with cervical cancer. All HV cause cells to synthesize DNA and undergo mitosis, and they can transform normal cell from many species to cells with malignant properties. (1 refs)

78-6684 **Epidermodysplasia Verruciformis. An Autoso mal Recessive Disease Characterized by Viru Warts and Skin Cancer. A Model for Viral Oncogenesi** (Eng) Lutzner, M. A. (Dermatology Branch, Room 23 I 238, Building 10, NCI, NIH, Bethesda, MD, 20014). *Bu Cancer (Paris)* 65(2): 169-182; 1978.

The case reports of 147 epidermodysplasia verruciform (EV) patients comprising 125 families were reviewed. EV an autosomal recessive disease that usually begins in infanc or childhood, with an av age of onset of 9. It was found tha EV has no racial predisposition and no geographic prefe ence, and it occurs with the same frequency in both sexe

warts are most common, but pityriasis-like warts occur prox 75% of patients. The warts are disseminated and ic. Cancer may develop as early as age 13; the av age set is 31. About one-third of the patients develop cancer e skin, usually in exposed areas. The cancer is often ple. The av time from wart to cancer is 24 yr, but cancer eveloped in as little as 2 yr. Malignant transformation s in carcinoma-in situ of the Bowenoid type or squa- cell carcinoma. Two deaths occurred by local invasion; one metastasis was recorded. One patient died of Bur- lymphoma and another was reported to have dis- ated reticulosis. Approx 8% of the patients are mental- arded. Humoral immunity is normal, but cell-mediated unity is depressed in most patients. The gene defect in as not yet been uncovered. (135 refs)

685 **Hepatocellular Carcinoma and the Hepatitis B Virus: Evidence for a Causal Association.** (Eng) ness, W. (Lab. Epidemiology, New York Blood Center, York, NY). *Prog Med Virol* 24: 40-69; 1978.

ence is presented in support of the hypothesis that titis B virus (HBV) is a primary etiological agent in the opment of hepatocellular carcinoma (HCC). HCC is spread in parts of Africa and southeast Asia, but relative- common in the US and other Western countries. Pa- s in the high-incidence areas are quite young, and they redominantly male. The hypothesis is supported by the arity in the geographic distribution of HCC and HBV, idenced by radioimmunoassay of the HBV surface anti- HBsAg). Moreover, there is an unusually high frequency BsAg and antibody to the hepatitis B core antigen (an- Bc) in HCC patients; the amount of free circulating sur- antigen seems to be relatively low. Based on available mation, the relative risk of past HBV infection in HCC nts is 1.0-1.5 in high-incidence areas and 10-15 in ncidence areas, 10-15. HBsAg prevalence in high-inci- e areas appears to be inversely related to patient age, and ner-child transmission is suspected. Although HCC is gly associated with the HBsAg carrier state, genetic and ronmental factors (eg, malaria, malnutrition) may also ribute to susceptibility to HCC. (114 refs)

686 **Epigenetic and Viral Aspects of Cancer: Group Report.** (Eng) Weiss, R. A. (Imperial Cancer Fund Labs., Lincoln's Inn Fields, P.O. Box 123, London A3PX, England); Baserga, R. L.; Basilico, C.; Bernhard, .; Bustan, H.; Gardner, R. L.; Green, H.; Illmensee, K.; isch, R.; Kaplan, H.; Koprowski, H.; Lilly, F.; McGuire, .; Pollack, R. E.; Sato, G. H.; Weissman, I. L. *In: Neo- ic Transformation: Mechanisms and Consequences. Pro- ings of a Meeting held by the Dahlem Workshop on Neo- ic Transformation: Mechanisms and Consequences in in, May 9-13, 1977.* Dahlem Workshop on Neoplastic sformation: Mechanisms and Consequences (Berlin, W. nany): 314 pp.; 269-288; 1977.

Epigenetic and viral hypotheses of carcinogenesis are summarized. Teratocarcinoma development usually involves transformation from a malignant pleuripotent stem cell to nonmalignant, differentiated progeny. This reversibility of the neoplastic state is an interesting concept for further research, especially since several human tumors of fetal origin, including retinoblastoma and Wilms' tumor, frequently regress postnatally. There is evidence that hormones play a role in tumor development, perhaps by activating an oncogene. Recent developments in culture methods are clarifying hormone requirements and interactions in neoplastic cell lines. Transformation by oncogenic DNA viruses appears to require the synthesis of specific viral gene products, with integration of the viral genome or genome fragments being essential for persistance of the transformed state. Papovaviruses, whose early genome region codes for both large T (tumor) and small t antigens, cause parotid gland tumors in animals and benign warts in humans. Most transforming RNA viruses (retroviruses) carry the oncogene *sarc*, but their replication is dependent on helper viruses that possess all virion genes. Although simian sarcoma helper virus and baboon endogenous virus have been isolated from humans, they have not been implicated in human disease. Papilloma virus, the cause of warts, is the only virus known to cause tumors in humans. (13 refs)

78-6687 **Tumor Phenotype and Progression: Group Report.** (Eng) Eichmann, K. P. (Institut fur Immunologie und Genetik, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, 6900 Heidelberg, W. Germany); Askonas, B. A.; Franke, W. W.; Howard, J. C.; Lennox, E. S.; Mitchison, N. A.; Nicolson, G. L.; Ohno, S.; Rajewsky, K. *In: Neoplastic Transformation: Mechanisms and Consequences. Proceedings of a meeting held by the Dahlem Workshop on Neoplastic Transformation: Mechanisms and Consequences in Berlin, May 9-13, 1977.* Dahlem Workshop on Neoplastic Transformation: Mechanisms and Consequences (Berlin, W. Germany): 314 pp.; 289-304; 1977.

Information concerning the phenotype of malignant cells and the immune reaction to malignant cells is reviewed. Topics discussed include the morphologic and biochemical properties of the tumor cell membrane, the three-dimensional arrangement of the malignant cells, characteristics of tumor cells with a high rate of metastasis, genetic characteristics of malignant cells, tumor cell antigens, and the biological function of antigens. A review of host responses to tumors includes immune surveillance, the role of immunity in metastasis, the association between the presence of histocompatibility antigens and susceptibility to tumors, manipulation of the immune system (ie, enhancement of tumor immunogenicity, stimulation of lymphocyte compartments, and idiotype manipulation), nonspecific defense mechanisms, and tumor-associated antigens. (22 refs)

78-6688 **Immune Surveillance.** (Eng) Howard, J. C. (Dept. Immunology, ARC Inst. Animal Physi-

ology, Brabraham, Cambridge CB2 4AT, England). *In: Neoplastic Transformation: Mechanisms and Consequences. Proceedings of a Meeting held by the Dahlem Workshop on Neoplastic Transformation: Mechanisms and Consequences in Berlin, May 9-13, 1977.* Dahlem Workshop on Neoplastic Transformation: Mechanisms and Consequences (Berlin, W. Germany): 314 pp.; 227-245; 1977.

The "strong" form of the immunosurveillance theory is discussed. This theory differs from weaker versions in asserting that the "true" tumor incidence in animals endowed with an immune system is higher than the observed incidence and that the difference is accounted for by the activity of the immune system in recognizing new antigens on incipient neoplastic cells and disposing of the cells that bear them. Two statements must be true for the strong theory of immune surveillance to be valid: (1) immunodepression will lead to an increase in the incidence of tumors in any age class; and (2) incipient neoplasias will be immunogenic. The concept has not stood up to experimental test. A generalized increase in spontaneous tumor incidence is not seen in experimental or natural states of immunodepression. Even highly immunogenic tumors are no more easily induced in immunodepressed animals than in normal controls. Only virus-induced cancers show an increased incidence in immunodepressed animals, just as such animals are most susceptible to nononcogenic viral infections. There is no evidence that the incidence of overt cancer is limited by the activity of the immune system except in the case of horizontally transmitted oncogenic viruses. It is worth wondering why immune surveillance is not effective in other situations in which tumors are highly antigenic. (25 refs)

78-6689 **Some New Data on the Pathogenesis of Chronic Lymphoid Leukemia (Meeting Abstract).** (Rus) Polianskaia, A. M. (No affiliation given). *Vopr Onkol* 24(9): 121; 1978. (no refs)

78-6690 **Mechanisms of Tumor Immunity.** (Eng) Cohen, S. (Dept. Pathology, Univ. Connecticut Health Center, Farmington, CT, 06032); Cohen, M. *Am J Pathol* 93(2): 449-457; 1978.

Ways in which the immune response system is able to effect the proliferation of tumor cells are reviewed. The immune mechanisms of tumor-cell killing are divided into two groups: cell-mediated and non-cell-mediated mechanisms. Effector cells in tumor cell-mediated destruction include lymphocytes, which secrete soluble mediators, participate in antibody-dependent reactions, and can become cytotoxic themselves; macrophages, which may be rendered cytotoxic by an arming factor from activated T lymphocytes; and granulocytes, which participate in antibody-dependent cytotoxic reactions. Noncellular mechanisms of tumor-cell destruction include lymphotoxins, produced by lymphocytes stimulated with specific antigen or with nonspecific mitogens that can kill or damage various cell lines in vitro; and complement, which can induce holes or lesions in the cell membrane of tun cells. Noncytotoxic effects of the immune system invo modification of cell mobility (important in metastasis and loss of contact inhibition). Although many natural protect measures are built into the immune system, genetic and oth predisposing factors can affect tumor resistance. (27 refs

78-6691 **Evolutionary Development of IgE and the R of Anaphylactic-Type Reactions in Resista to Solid Tumours.** (Eng) Lynch, N. R. (Institut de l che·ches Scientifiques sur la Cancer, B.P.N 8, 94800 Villej France); Salomon, J. C.; Turner, K. J. *Cancer Immunol munother* 4(4): 223-228; 1978.

The evolutionary development of IgE and the role of a phylactic reactions in resistance to solid tumors are review The necessary components for allergic or anaphylactic-t reactions are found in many species, including marsupi which have long diverged from the main mammalian li This finding suggests that the existence of such reactions been evolutionarily conserved, and thus may have a regula ry or protective role in the organism. Evidence suggest that anaphylactic-type reactions are a constituent of ti-tumor mechanisms is presented. These reactions can crease the access of immune effectors into solid tumors, though progressively growing tumors appear to have self-protective mechanism inhibiting such reactions. It not yet been established that the anaphylactic system direc modulates the activity of lymphoid cells, although invol ment in the expression of delayed hypersensitivity seems c tain. The possiblity that anaphylactic-type reactions contr ute to parasite rejection is an attractive but controversial id (79 refs)

78-6692 **Immunology of Rat Hepatic Neoplasia.** (E Baldwin, R. W. (Cancer Res. Campaign La Univ. Nottingham, Nottingham, England). *In: Rat Hep Neoplasia: Workshop on Rat Liver Neoplasia held by Will F. Merrell, Co. in Woods Hole, October, 1974.* William Merrell, Co. (Woods Hole, MA): 288 pp.; 228-240; 197

The expression of tumor-associated rejection antigens, mor-specific cell-surface antigens, and tumor-associa embryonic antigens in carcinogen-induced rat liver tum is discussed. The most significant characterisic of carci gen-induced tumors is expression of the tumor-spec cell-surface antigens that may function as tumor-rejecti antigens. This type of neoantigen is not always expressed transformed cells and cannot be used as a criterion of ma nant change. However, there are few exceptions to the ge al finding that each tumor has a characteristic antigen, characterization of this specificity may be useful in evaluat the role of carcinogenic agents in transformation. Embryo antigen expression may be a concomitant effect of neopla change; thus, typing of these antigens could provide a suita preliminary screening assay for carcinogen-induced transl mation. The role of these antigens in tumor rejection is resolved, but it is unlikely that they are responsible for

ty elicited against transplanted hepatic tumors. (31 refs)

593 **On the Pathogenesis of Cutaneous Malignant Lymphoma (CML).** (Ger) Steigleder, G. K. versitat Hautklinik Koln, Joseph-Stelzmann-Strasse 9, Koln 41, W. Germany). *Z Hautkr* 53(20): 719-726;

eviously published suggestion concerning the pathogene- cutaneous malignant lymphoma (CUML) is discussed. suggestion still appears valid in view of current observa- Both T- and B-cell lymphomas of the skin have been ted. The suggested model of CUML development in- s proliferation of lymphocytes stimulated by persistent gy or chronic exposure to UV light; if a lymphocyte con- neoplastic information, a clone of neoplastic cells will e. The stimulated lymphocytes secrete lymphokinin, h influences other cells (eg, by decreasing the movement acrophages). Because T-lymphocytes are more common B-lymphocytes, neoplastic transformation of T-lym- ytes is more probable. Mycosis fungoides (MF) can be ded as analogous to eczema, while B-cell CUML can onsidered a type of exanthema. The involvement of nic allergy is consistent with the association of MF with in occupations such as construction work and others ng to sun exposure. In this model, infectious mononu- is is considered a pseudolymphoma. (43 refs)

694 **Antigenic Changes in the Transformed Cell.** (Eng) Lennox, E. S. (MRC Lab. Molecular Bi-, Hills Road, Cambridge CB2 2QH, England); Sikora, *n: Neoplastic Transformation: Mechanisms and Conse- ces. Proceedings of a Meeting held by the Dahlem Work- on Neoplastic Transformation: Mechanisms and Conse- ces in Berlin, May 9-13, 1977.* Dahlem Workshop on lastic Transformation: Mechanisms and Consequences in, W. Germany): 314 pp.; 197-207; 1977.

effect of the immune system on antigenic changes in the ce components of transformed cells was studied. Tumor ens are defined by various modes of immune response em: in vivo by induction of transplantation immunity or ed-type hypersensitivity and in vitro by serological or nediated reactions against tumor cells as targets. By uring these separate modes of response, various antigens e defined on the same tumor. The following antigens e detected on tumor cells, some unique, some shared normal cells: (1) normal transplantation antigens (the r targets of immune rejection reactions when tissue is planted between individuals); (2) tumor-specific tran- tation antigens (TSTA: defined in protection assays in h animals immunized with the tumor are subsequently enged with the same or other tumors, with studies re- ng that certain induced tumors carry unique TSTA); (3) -determined antigens (those of DNA and RNA tumor es; they can serve as transplantation antigens as well as unogens for antibody formation and thus may be targets umoral as well as cell-mediated attack); (4) embryonic antigens (defined by antisera prepared in syngeneic animals by injection of preparations of mid-term embryos or by sera from multiparous animals; they can detect antigens on tumor cells transformed by viruses or induced by carcinogens); and (5) differentiation antigens (those present on most cells of one particular individual). TSTA appear to be the most likely candidates for recognition in immune surveillance, and they may play a major role in the interaction between the immune system and cells undergoing transformation. (12 refs)

78-6695 **Immunodeficiency and the Pathogenesis of Lymphoma and Leukemia.** (Eng) Louie, S. (Tufts Univ. Sch. Medicine, Boston, MA, 02111); Schwartz, R. S. *Semin Hematol* 15(2): 117-138; 1978.

The possible pathogenic connection between immunologic abnormalities and malignant lymphoproliferative diseases is examined in light of clinical situations associated with a high risk of lymphoma. Several congenital immunodeficiency diseases are associated with a high risk of malignant lymphoma: ataxia telangiectasia, Wiscott-Aldrich syndrome, common variable immunodeficiency, and Bloom's syndrome. A characteristic of all these diseases is the presence of abnormalities outside the immune system, and the genetic disturbance in these conditions can manifest itself by structural changes in chromosomes. These diseases may be regarded as premalignant states characterized by chromosome instability and an associated immunologic disturbance. The risk of developing malignant lymphoma is also increased in recipients of renal allografts and in untreated patients with certain immunoinflammatory diseases (autoimmune hemolytic anemia, Sjogren's syndrome). The risk of developing acute myelogenous leukemia is increased in patients treated with immunosuppressive agents for immunoinflammatory diseases and in cancer patients treated with either aggressive chemotherapy or chemotherapy combined with radiotherapy. It is suggested that some 'spontaneous' lymphomas may arise as the result of the enhanced proliferation of mutant lymphocytes brought about by the selective pressure of impaired immunoregulation. (164 refs)

78-6696 **Geographical Distribution of Gastrointestinal Cancer and Breast Cancer and Its Relation to Selenium Deficiency.** (Eng) Jansson, B. (Natl. Large Bowel Cancer Project, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030); Malahy, M. A.; Seibert, G. B. *In: Third International Symposium on the Detection and Prevention of Cancer held by the International Study Group for the Prevention and Detection of Cancer in New York, April 26-May 1, 1976.* International Study Group for the Prevention and Detection of Cancer (New York, NY): Vol. 1(part 1): 1193 pp.; 1161-1178; 1977.

Evidence indicating that selenium may act as an inhibitor of cancer of the colon, rectum, and breast is reviewed. Studies in the US and New Zealand showed that low rates of colon, rectal, and breast cancer were associated with high Se concen-

trations in the soil and vice versa. A New Zealand veterinarian observed that the incidence of intestinal adenocarcinomas and other neoplasms in sheep was reduced after the introduction of Se drenching. Similar findings were obtained in studies of rats fed carcinogens with and without Se. Another study showed that spontaneous mammary tumors were inhibited by Se in mice. An unexpected finding was that the incidence age was lowered for tumor-bearing mice fed Se compared with untreated control tumor-bearers. Se deficiency reduces the fertility of animals and may also have the same effect in humans. Thus, the finding of a negative correlation between birth rates and colon, rectal and breast cancer rates in a study of the natality and mortality statistics for 48 continental states further supports the hypothesis that Se or some other agent acts as an inhibitor of these cancers. (38 refs)

78-6697 **Causes of Cancer in Man.** (Eng) Miller, R. W. (NCI, NIH, Bethesda, MD, 20014). *In: Neoplastic Transformation: Mechanisms and Consequences. Proceedings of a Meeting held by the Dahlem Workshop on Neoplastic Transformation: Mechanisms and Consequences in Berlin, May 9-13, 1977.* Dahlem Workshop on Neoplastic Transformation: Mechanisms and Consequences (Berlin, W. Germany): 314 pp.; 25-38; 1977.

The causes of cancer in humans are reviewed, with emphasis on physical and chemical carcinogens. Among the physical carcinogens are two forms of radiation, ionizing and UV. Ionizing radiation can penetrate deeply and induce various forms of cancer, whereas UV light is not penetrating and induces only skin cancer. Asbestos acts as a physical carcinogen in that its physical properties, ie, the length and diameter of the fibers, apparently account for its carcinogenicity in various organs. Chemical carcinogens induce respiratory tract, urinary bladder, blood, and liver malignancies, especially in heavily exposed industrial workers. A subtle influence of chemical carcinogenesis early in life is indicated by the retention of old-country cancer rates in migrants whose children have the cancer rates of the new country and by the distinctive patterns of excessive mortality from specific cancers observed in the 3,056 US counties between 1950-1969. Some of these patterns appear to be related to industries within the counties. Despite extensive laboratory evidence for viral oncogenesis, no virally induced human cancers have been demonstrated. Host factors, including single genes, chromosomal aberrations, and immunodeficiency, may place individuals, families, or ethnic groups at a very high or low risk of certain cancers. (33 refs)

78-6698 **Variations in Cancer Death Rates.** (Eng) Lew, E. A. (Dept. Epidemiology and Statistics, American Cancer Society, Inc., New York, NY). *In: Third International Symposium on the Detection and Prevention of Cancer held by the International Study Group for the Prevention and Detection of Cancer in New York, April 26-May 1, 1976.* International Study Group for the Prevention and Detection of Cancer (New York, NY): Vol. 1(part 1): 1193 pp.; 1127-1138; 1977.

Current observations of the variations in cancer death ra among various populations are reviewed briefly, with a wa ing directed against premature overzealous interpretation apparent differences. Although US death rates increas 5.2% in the first 7 mo of 1975, the age-adjusted death r actually increased only approx 1% over the entire yr. It been an observable phenomenon, however, that sharp creases are noted in cancer death rates over the first half any year. Comparisons among nations must be made w care, particularly when 10-fold differences in population s exist, eg, the US and Sweden. Moreover, methods of de certification and registration vary from country to count automatically introducing bias. It is suggested that it may at least as useful to study mortality rates from different pa of the US as to compare different countries. Several spec studies investigating social factors are discussed; in gene it has been found that death rates from most cancers higher for the lower socioeconomic classes (as defined by cupation, education, and/or economic status), although opposite is true for prostate cancer and leukemias in men a breast cancer in women. Studies of native white vs reign-born white vs nonwhite populations have also been u ful in determining several interesting relationships, such the increased digestive tract cancer and decreased prost cancer mortality in these non-native populations. Bet medical care facilities will continue to improve both tun classification and the definition of various cancer inciden and mortalities. (no refs)

78-6699 **Our Daily Habits and Cancer.** (Swe) Werko, (Farmacevtisk Divisionen, Astra Lakeme AB, Sweden). *Lakartidningen* 75(10): 919-920; 1978.

The risk of cancer is increased by tobacco, alcohol, and tary habits. Positive correlations have been found betw alcohol consumption and laryngeal and buccal cavity can and between high-fat diets and leukemia or colon and bre cancer. (11 refs)

78-6700 **Benign and Malignant Breast Tumou Epidemiological Similarities.** (Eng) Sartwell E. (Dept. Epidemiology, Johns Hopkins Univ. Sch. Hygi and Public Health, Baltimore, MD, 21205); Arthes, F. Tonascia, J. A. *Int J Epidemiol* 7(3): 217-221; 1978.

Risk factors were estimated in 783 cases of cystic diseas the breast (CD), 155 cases of breast fibroadenoma (FA), cases of miscellaneous breast conditions, and 284 cases breast cancer. FA occurred in the youngest patients, the hi est percentage (39.4%) occurring in patients aged 15-24 The cancer patients were the oldest, 67.6% of the cases oc ring in women aged 45-64 yr. Relative risks were calcula for each of the four breast conditions, with respect to possible risk factors that could be categorized dichotomou These were nulliparity, first pregnancy at age 25 or ol being premenopausal at the time of discovery of the les and marriage at age 20 or over. Each patient was compa

her own control matched for age, race, ever-married s, time of hospitalization, and pay status. Risks associat- th being nulliparous were all above unity, but only that e cancer patients was statistically significant ($p < 0.05$). irst pregnancy at an older age, all the risks were above , and those for CD and cancer were significantly elevat- n all four disease classes, the patients had fewer pregnan- han their controls; the differences were significant only D and FA. CD patients had experienced both natural rtificial menopause less commonly than their controls; r patients had experienced only artificial menopause, ommonly than their controls. This general similarity en benign breast disease and breast cancer in certain ductive and menstrual features plus previous evidence reast cancer is more frequent in women who have previ- enign breast disease suggest a similarity in etiologic fac- (9 refs)

701 **The "Urban Factor" and Lung Cancer: Cigarette Smoking or Air Pollution?** (Eng) Carnow, . (Dept. Preventive Medicine, Univ. Illinois, Chicago, 0680). *Environ Health Perspect* 22: 17-21; 1978.

nce that urban pollution is a significant etiologic factor g cancer was provided by four groups of studies. Studies ban-rural death rates revealed a doubling of lung cancer ality in large cities compared with rural areas, which not be explained by a difference in smoking habits. es of lung cancer death rates in migrants also suggested lationship to urban pollution. Among studies that regression analysis in an attempt to identify urban rs responsible for urban-rural differences in death from lung carcinoma, one indicated that the ucts of solid fuel combustion may be an important ogic factor and another showed a significant re- nship between the death rates and atmospheric o(a)pyrene (BP) levels. After standardization uch variables as smoking habits, age, sex, and dura- f residence, sampling studies in the US and other coun found that lung cancer incidence was significantly iated with urbanization and air pollution. Data on lung r deaths among coke oven workers were used to calcu- dose-response relationship between BP and lung cancer s in an urban community. The risk of excess lung cancer s due to continuous exposure to BP is higher than previ- assumed. (24 refs)

702 **Identification of Carcinogenic Hazards from Aromatic Amine Exposures and Measures for ol.** (Eng) Parkes, H. G. (Health Res. Unit, British Rub- Manufacturers' Assoc., Scala House, Holloway Circus, ingham 5, England). *In: Prevention and Detection of er. Proceedings of the Third International Symposium on tion and Prevention of Cancer Held by the International Group for the Detection and Prevention of Cancer in York, April 26 - May 1, 1976.* International Study Group he Detection and Prevention of Cancer. (New York, Vol. 2(part 1), 2404 pp.; 1913-1920; 1978.

Variation in the duration, intensity, and conditions of occupational exposure to carcinogens such as aromatic amines will determine whether the resultant cancer incidence is 100% or negligible. Suspicions may be aroused by chemical similarities between established and suspect carcinogens and they may be reinforced by evidence of experimental mutagenicity, teratogenicity, or carcinogenicity, but positive epidemiological identification is the final confirmation of a carcinogenic hazard. (12 refs)

78-6703 **Cell Cycle Dependency of Transformation.** (Eng) Baserga, R. L. (Dept. Pathology, Fels Res. Inst., Temple Univ. Sch. Medicine, Philadelphia, PA, 19140). *In: Neoplastic Transformation: Mechanisms and Consequences. Proceedings of a meeting held by the Dahlem Workshop on Neoplastic Transformation: Mechanisms and Consequences in Berlin, May 9-13, 1977.* Dahlem Workshop on Neoplastic Transformation: Mechanisms and Consequences (Berlin, W. Germany): 314 pp.; 125-133; 1977.

A review of the major studies concerning the cell-cycle dependency of transformation, coupled with more recent work showing a close relationship between transformation and mutagenesis, suggest that G_1 cells are more susceptible to transformation than are G_0 cells because they have a higher relative transcriptional activity, and transcriptionally active chromatin is more accessible to mutagens and carcinogens than is transcriptionally inactive chromatin. It has also been shown that S-stage cells are susceptible to transformation for the same reason G_1 cells: incorporation of the transforming agent into the accessible DNA. It may be predicted from these conclusions that G_0 cells are strongly resistant to transformation by chemical carcinogens, and research is discussed that supports this contention. (18 refs)

78-6704 **DNA Polymerase and Mutation.** (Eng) Bridges, B. (Univ. Sussex, Sussex, England). *Nature* 275(5681): 591-592; 1978.

Several theories on the interaction between DNA damage and DNA polymerases in the generation of permanently altered nucleotide sequences and, as a result, cancer and certain heritable diseases are presented. (4 refs)

78-6705 **Cellular Susceptibility to Neoplasia and Its Reversibility.** (Eng) Gardner, R. L. (Dept. Zoology, Univ. Oxford, South Parks Road, Oxford OX1 3PS, England). *In: Neoplastic Transformation: Mechanisms and Consequences. Proceedings of a Meeting held by the Dahlem Workshop on Neoplastic Transformation: Mechanisms and Consequences in Berlin, May 9-13, 1977.* Dahlem Workshop on Neoplastic Transformation: Mechanisms and Consequences (Berlin, W. Germany): 314 pp.; 111-124; 1977.

Cell susceptibility to neoplastic transformation and its reversibility are reviewed. The susceptibility has been proven to be

dependent on both intrinsic and extrinsic elements. Intrinsically, genetic manifestation of susceptibility is the result of polymorphic loci coding for enzymes involved in DNA repair or metabolism of carcinogens and proteins affecting the activity of tumor viruses. Among the extrinsic factors that have been implicated in neoplasia because they alter the cellular environment are chemical carcinogens, 'foreign bodies', prolonged endocrine imbalances, and other elements that impose stress on tissue homeostasis. It is suggested that all these extrinsic mechanisms act by stimulating cell division. A number of methods have been used to suppress neoplasticity; such as incorporation of a thymidine analog into DNA, use of temperature-sensitive mutant cells that are neoplastic only at the permissive temperature, or hybridization of malignant cells with nonmalignant cells that have lost a single chromosome. Differentiation of tumor cells to a terminal, postmitotic state can result in loss of neoplasticity. Furthermore, a model of plant and animal teratoma cells and nuclei isolated from adenocarcinoma cells suggests that neoplasia may in some instances also be reversed. (33 refs)

78-6706 **Characterization of Hepatic Nodules.** (Eng) Becker, F. F. (Dept. Anatomic and Experimental Pathology, M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030). *In: Rat Hepatic Neoplasia: Workshop on Rat Liver Neoplasia held by William F. Merrell, Co. in Woods Hole, October, 1974.* William F. Merrell, Co. (Woods Hole, MA): 288 pp.; 42-57; 1978.

Research on premalignant and malignant hepatic nodules is reviewed. Identification of premalignant lesions in animal tissues exposed chronically to chemical carcinogens would provide insight into the possibility of a chemical etiology for similar lesions in humans, allow analyses to be focused on one small region rather than the entire organ, and would help in understanding of characteristics of malignant cells. Evidence indicating that hepatic nodules are premalignant lesions is presented. Study of hepatic nodules allows carcinogen-altered tissue to be examined at various stages in its progression toward malignancy and nodules of different stages to be compared with each other and with nonnodular parenchymal areas. Techniques allowing cytogenetic analysis of the chromosome composition of solid hepatic tissues have been developed recently. Problems in transplanting of hepatic nodules successfully are reviewed. The hepatic nodule is the best available tissue to which new analytical techniques can be applied and upon which new oncological concepts can be tested. (35 refs)

78-6707 **Sequential Cellular Alterations During Hepatocarcinogenesis.** (Eng) Bannasch, P. (Abteilung fur Cytopathologie, Institut fur Experimentelle Pathologie Deutschen Krebsforschungszentrum, Heidelberg, W. Germany). *In: Rat Hepatic Neoplasia: Workshop on Rat Liver Neoplasia held by William F. Merrell, Co. in Woods Hole, October, 1974.* William F. Merrell, Co. (Woods Hole, MA): 288 pp.; 58-99; 1978.

The sequential alterations observed in liver cells under th influence of hepatocarcinogens are discussed. Reversible a terations are characterized by a predominantly centrilobul loss of glycogen and by a concomitant dispersal of the bas phílic bodies. The outstanding feature of persistent alter tions is an excessive storage of glycogen, which appears be due to the direct action of the carcinogen, resulting in irreversible cell lesion. At the end of the preneoplastic pha in most animals, so-called hyperplastic nodules develop. Th nodules appear to originate from areas storing glycogen excess, and most nodules are probably a mixture of preca cerous, cancerous, and diverse intermediary cells. It is high probable, however, that the hyperplastic nodule is only o of at least two histologically different formations in whi neoplastic transformation can take place. Nearly the enti liver parenchyma appears to undergo irreversible cellular terations, with cellular enlargement being due mainly excessive glycogen storage and/or a proliferation of the mem branes of the agranular endoplasmic reticulum. The data su gest that the glycogen-free basophilic tumor cell is the resu of a long process that begins with an excessive storage glycogen and perhaps passes through a stage of membra proliferation or fat accumulation. (67 refs)

78-6708 **Characteristics of Malignant Phenotypes Familial Polyposis.** (Eng) Wells, S. A. (Du Univ. Medical Center, Durham, NC, 27710); Johnson, A. H Gregory, R. O. *In: International Advances in Surgical O cology.* Murphy, G. P., ed. (New York: Alan R. Liss, Inc Vol 1, 288 pp.; 29-52; 1978.

The clinical characteristics of various gastrointestinal polyp sis syndromes, particularly familial polyposis coli (FPC), a their relationship to colorectal cancer are reviewed. FP which is transmitted as an autosomal dominant trait, is ch racterized by development in adolescence or early adult l of adenomatous polyps on the mucous membrane of the col and rectum. The incidence of colon malignancy in FPC thought to approach 100%. Proper therapy is contingent distinguishing the disease from inflammatory polyps, ly phoid polyps, hamartomatous polyps, multiple neuro bromatosis (Von Recklinghausen's disease), lipomatous p lyps, hyperplasia or metaplasia, and pneumatosis cystoi intestinalis. There are no serum, plasma, blood cell, or uri markers associated with the disease. Surgery is the treatme of choice, the most common procedures being total pro tocolectomy with abdominal ileostomy, total colectomy a ileoproctoscopy (TC and I) (preferred), or anal ileostom Regression of rectal polyps occurs in approx 10%-15% FPC patients undergoing surgery, but this phenomenon is n permanent. Other syndromes that share two common tra with FPC (autosomal dominant inheritance and propens to develop gastrointestinal carcinoma) include Gardne syndrome, Turcot's syndrome, familial 'minor' adenomato polyposis coli, juvenile polyposis coli, and Peutz-Jeghers sy drome. The etiology of all these syndromes may involve ge etic, environmental, and immunologic factors. (91 refs)

709 **Gas Standards for Air Pollution Analysis.** (Eng) Taylor, J. K. (Natl. Bureau Standards, Gaithers- MD); Hughes, E. E.; Dorko, W. D.; Cadoff, B. C.; idt, W. P.; Marinenko, R. J.; Friend, D. G.; Meeks, S.; de, E.; Johns, R. H.; Deardorff, E. R.; Friend, D. G.; er, B.; Heinrich, K.; Myklebust, R. *NBS Tech Note* : 80-104; 1978.

rch was conducted to develop or improve methods for ring primary gas standards for air pollution analyses by metric, volumetric, and manometric techniques. Anoth- jective was to provide the traceability of all air pollution urements, including those concerned with the occupa- l environment, ambient air, and source emissions, to a ion set of analytical standards. (8 refs)

710 **Applications of Infrared Measurements to Air Pollution Problems.** (Eng) Deslattes, R. (Natl. u Standards, Gaithersburg, MD); Howard, C. J.; Rad- H. E.; Lafferty, W. J.; Freund, S.; Layer, H.; Schenck, ougen, J.; Maki, A.; Beers, Y.; Evenson, K.; Wells, J. evoe, J.; Sweger, D.; Hughes, E.; Okabe, H.; Streit, G. *BS Tech Note* (963): 22-36; 1978.

niques and instrumentation were developed to utilize nd infrared laser devices in measuring air pollutants, cularly NO_2 and O_3, and molecules that play a role in ollution, OH and HO_2. The latter two molecules are al species in the chemistry of smog formation and spheric ozone destruction by anthropogenic pollutants. fs)

711 **In Vivo Covalent Binding of Chemicals to DNA as a Short-Term Test for Carcinogenicity ting Abstract).** (Eng) Lutz, W. K. (Inst. Toxicology, /Univ. Zurich, CH-8603 Schwerzenbach, Switzerland); tter, C. *Experientia* 34(7): 927; 1978. (no refs)

712 **Effects of Vinyl Chloride in Man. A Cytogenetic Follow-up Study.** (Eng) Hansteen, I. L. (Lab. tics, Telemark Central Hosp., Olavsgt. 26, 3900 Porsg- Norway); Hillestad, L.; Thiis-Evensen, E.; Heldaas, S. *utat Res* 51(2): 271-278; 1978.

ond cytogenetic study was made of 37/39 workers at vinyl chloride plant 2.5 yr after a first study, during time the workers had minimal exposure to vinyl chloride monomer (VCM). The second study, performed with 32 matched controls, was conducted to determine whether the chromosome damage found in the first study was due to VCM. Of the original 39 workers, 14 had been chosen at random, 13 because they had heavy exposure to VCM for years, and 12 because of abnormal clinical findings that later proved to be normal. Breaks, gaps, and stable rearrangements were scored as 100 metaphases/person from 48-hr lymphocyte cultures. In the first study, the mean number of chromosome breaks was significantly higher for the workers (3.41%) than for the controls (1.79%). No significant difference between these groups was found in the second study. In addition, there was no significant difference in mean number of breaks between the first control group and both groups of the second study. The results of the two studies provide evidence that VCM was the cause of the chromosome damage found in the first study. In the second study, the mean number of sister chromatid exchanges per cell was the same (7.6) for both workers and controls. (19 refs)

78-6713 **Hepatic Angiosarcoma due to Vinyl Chloride. Report of 4 Cases.** (Fre) Roche, J. (Clinique d'Hepatologie-Gastroenterologie, C.H.U. de Grenoble, Hopital des Sablons, F 38700 La Tronche, France); Fournet, J.; Hostein, J.; Panh, M.; Bonnet-Eymard, J. B. *Gastroenterol Clin Biol* 2(8/9): 669-678; 1978.

Angiosarcomas of the liver developed in four men (aged 63, 48, 38, and 42 yr) who had worked in the production of vinyl chloride (VC) for 12, 26, 10, and 12 yr, respectively. Initial symptoms were abdominal pain in three patients and back pain (due to metastases) in one. The most constant laboratory indication was elevated serum alkaline phosphatase [55-77 milli(m)IU]; gamma-glutamyltranspeptidases were markedly elevated (217 and 298 mIU) in the two patients in which they were measured. α-Fetoprotein was normal, and SGOT and SGPT were close to normal. Two patients had hepatomegaly, which was the principal clinical finding in the literature on other VC-induced angiosarcomas. Arteriography revealed the angiosarcoma in the four patients, although ^{99m}Tc liver scans in two patients were also indicative of liver pathology. Gastrointestinal tract hemorrhage occurred in two patients and hemorrhage into the peritoneum in two. Survival from onset of symptoms was 2-13 mo. Clinical, biochemical, and histological features of previously reported patients with VC-induced angiosarcomas are reviewed. (50 refs)

78-6714 **Occurrence of Hepatocellular Tumors and Hemangiosarcoma in Rats Inhaled 1,2-Di-**

bromoethane Under the Influence of Disulfiram Treatment (Meeting Abstract). (Eng) Wong, L. C. (Pharmacology and Toxicology, Midwest Res. Inst., Kansas City, MO, 64110); Winston, J. M.; Hong, C. B.; Lee, C. C.; Bhandari, J. C. *Pharmacologist* 20(3): 174; 1978. (no refs)

78-6715 **Chromosomal Analyses in Vinyl Chloride-exposed Workers.** (Eng) Purchase, I. F. (Central Toxicology Lab., Central Medical Group and Mond Div., Imperial Chemical Industries Ltd., Alderley Park, Macclesfield, Cheshire, England); Richardson, C. R.; Anderson, D.; Paddle, G. M.; Adams, W. G. *Mutat Res* 57(3): 325-334; 1978.

The chromosomal morphology of cultured peripheral lymphocytes from 81 men [57 employed in plants manufacturing vinyl chloride (VC) or polyvinyl chloride (PVC), 19 on-site controls, and 5 off-site controls] was studied. There was a significant increase in chromosomal abnormalities among the VC/PVC-exposed workers compared with the controls. Total B cells (those with a chromatid break or gap or a chromosome gap), total Cu cells (those with larger unstable chromosomal abnormalities), and total Cs cells (those with larger unstable chromosomal abnormalities) showed the greater increases in autoclave operators, with smaller increases in the other five job categories. The increase in chromosomal aberrations was correlated with length of exposure and with a history of exposure to short-term excursion levels (approx 15 ppm) of VC during the year prior to sampling (1973-1974). There were no correlations between results of liver function tests and chromosome aberrations. Quantity of tobacco smoked 18 mo after blood sampling was correlated with total C cells, as was smoker vs nonsmoker status at 18 mo postsampling. It was not possible to determine whether smoking history, length of employment, or exposure to short-term excursion levels of VC was the most important variable in determining C-cell abnormalities. (15 refs)

78-6716 **Use of Terbium(III) Fluorescence Enhancement to Selectively Monitor DNA and RNA Guanine Residues and Their Alteration by Chemical Modification.** (Eng) Ringer, D. P. (Biomedical Div., Samuel Roberts Noble Foundation, Ardmore, OK, 73401); Burchett, S.; Kizer, D. E. *Biochemistry* 17(22): 4818-4825; 1978.

The abilities of DNA and ribosomal RNA (rRNA) from rat liver to enhance terbium(III) ($Tb^{3}+$) fluorescence were studied under aqueous conditions at pH 6 and at room temperature. DNA and rRNA excited by 290-nanometer light enhanced $Tb^{3}+$ fluorescence by 1,800-fold and 13,000-fold, respectively. Of various ribose and deoxyribose nucleotides examined, only those containing guanine, guanosine 5′-monophosphate (Guo-5′-P) and deoxy-Guo-5′-P, produced significant enhancement of fluorescence. Similarly, only poly(G) of the homopolymers of the four common ribonucle tides was a strong enhancer to $Tb^{3}+$ fluorescence. The Guo-5 P moiety in the polymer state was at least five to six tim more efficient in increasing fluorescence than the free nucle tide. No enhancement was produced with 7-methyl-Guo-5′ or Guo-5′-P modified at the 1 and N^2 positions by kethox and at the 8 position by N-acetoxy-2-acetylaminofluore (Na-AAF). Chemical modification of rat liver DNA a rRNA in vitro with NA-AAF resulted in a 70% and 30% respectively, reduction in their ability to enhance Tb^{3} fluorescence. Thus, $Tb^{3}+$ may be useful as a guanine-specif fluorescent probe for RNA and DNA. Also, since modific tions at several different positions on guanine caused loss enhancing ability, the terbium probe may be useful in dete ing guanine modifications. (40 refs)

78-6717 **Chemical and Toxicological Studies on Brack Fern, *Pteridium aquilinum* Var. *Latiusculu* I. Introduction, Extraction and Fractionation of Consti ents, and Toxicological Studies Including Carcinogenic Tests.** (Eng) Yoshihira, K. (Natl. Inst. Hygienic Scienc Kamiyoga-1-Chome, Setagaya-ku, Tokyo, Japan); Fukuol M.; Kuroyanagi, M.; Natori, S.; Umeda, M.; Morohoshi, Enomoto, M.; Saito, M. *Chem Pharm Bull (Tokyo)* 26(2346-2364; 1978.

Twenty-four pterosins and related compounds isolated fr Bracken Fern, *Pteridium aquilinum* var. *latiusculum*, w tested for toxicity in HeLa cells and experimental anima Young fronds and rhizosomes were collected from vari sites, extracted with organic solvents and/or water, and, some cases, further purified by column and thin-la chromatography. Typical isolates were a group of C_{14} or sesquiterpenoids with a 1-indanone nucleus, termed pter ins, and their related glucosides and pterosides. Several co pounds produced morphologic changes in HeLa cells w test samples for 3 days. In animal toxicity tests, the co pounds were administered to DDD mice, Wistar male r and male Hartley guinea pigs by feeding (5 or 15 g/day), injection (0.2 or 0.3 ml/20 g), or gastric intubation (0.4 ml/ g). Four of the pterosins were toxic for the mice as w several crude bracken fractions. A frequent finding was jury to actively dividing cells, including involution of thymus and cytotoxic changes in the lymph follicles crypts of the small intestine. Long-term carcinogenesis fe ing experiments were undertaken in male Wistar and Fisc rats, with 4-340 mg/day of fern isolates added to their d for 35-205 days. Crude extracts of fronds and rhizoso induced tumors preferentially in Fischer rats, particularl the ileum, but purified fractions and extracts did not. ileal tumors included adenomas and papillary carcino (49 refs)

78-6718 **Comparison of the Oncogenicities of F Structurally Isomeric N-Hydroxyxanthi**

) Teller, M. N. (Donald S. Walker Lab., Sloan-Kettering Cancer Res., 145 Boston Post Road, Rye, NY, 10580); inger, J. M.; Zvilichovsky, G.; Watson, A. A.; McDon- J. J.; Stohrer, G.; Brown, G. B. *Cancer Res* 38(7): -2042; 1978.

oncogenicities of all of the four possible isomeric ydroxyxanthines were compared in rats. 3-Hydroxyxan- e induced sarcomas in 88%-100% of the rats when ad- istered sc at a dose of 1 mg 3x/wk for 8 wk; at ose of 0.1 mg (same route and schedule), both omas and fibromas appeared in 25%-58% of the given the isomer. Total 3-hydroxyanthine doses ing from 12-66 mg/rat induced sc tumors in 25%- of the rats, some of which also developed hepato- lar carcinomas. The oncogenicity of 7-hydroxy- hine approached that of the 3-isomer, particularly e induction of liver tumors. At 1 mg given 3x/wk for , the 7-isomer induced both sc and liver tumors in 40% e rats compared with 89% for the 3-isomer. Liver tumors induced in 45% and 65% of the rats given 1.0-mg ip tions (3 x/wk for 8 wk) of the 7- and 3-isomers, respec- y. The difference was not significant. 9-Hydroxyxanthine ed no oncogenicity, which is the result of the stability sulfate ester. 1-Hydroxyxanthine was not oncogenic in ssay; it has induced tumors at doses > 1.0 mg, but there explanation for its oncogenicity by any correlation of emical properties with those of the 3- and 7-isomers. (25

719 **The Tumor Promoting Action of Diterpene Esters In Vivo Correlates with Their Potency to se Prostaglandins from Macrophages In Vitro (Meet- bstract).** (Eng) Brune, K. (Dept. Pharmacology, Bi- rum, CH-4056 Basel, Switzerland); Hecker, E. *Experi-* 34(7): 922; 1978. (no refs)

720 **Snuff and Cancer of the Oral Cavity.** (Swe) Axell, T. (Institutionen for oral kirurgi, Lunds uni- et, S-214 21 Malmo, Sweden); Mornstad, H.; Sund- , B. *Lakartidningen* 75(22): 2224-2226; 1978.

elationship between snuff and oral cancer was studied eries of 375 oral cancer patients found in Sweden during -1971. Forty-one patients admitted using snuff at the of diagnosis, 8 had been snuff-dippers, 18 denied ever snuff, and 109 admitted using tobacco in other ways; were no data on tobacco use for 199 patients. A rela- hip between snuff and cancer was documented in 14 and found probable in 19. In 67.3% of the verified -dippers, the cancer was localized to regions of the oral y where the snuff had been placed. Most patients, both ntire group and the snuff-dippers, were in the age brack- -80 yr. The percentage of snuff-related tumors increased advancing age. The findings indicate that snuff-dipping increases the cancer risk at the site where the snuff is placed five- to sixfold. (7 refs)

78-6721 **The Role of Aflatoxin in Primary Liver Cancer (Meeting Abstract).** (Eng) Pang, R. T. (Dept. Internal Medicine, Univ. Indonesia, Jalan Tanah, Abang Enpat, Indonesia). *In: Summary Program and Abstracts of Papers. Proceedings of the 3rd Asian Cancer Conference Held by the Philippine Cancer Society under the Auspices of the Asian Federation of Organizations for Cancer Research and Control in Manila, 26-30 September, 1977.* Philippine Cancer Society. (Manila, Philippines): 184 pp.; 39; 1977. (no refs)

78-6722 **Liver Carcinogenesis in Rats after Aflatoxin B_1 Administration. A Light- and Electron-Microscopic Study.** (Eng) Novi, A. M. (Pathologisches Institut, Universitat Dusseldorf, Moorenstrasse 5, D-4000 Dusseldorf, W. Germany). *Curr Top Pathol* 65: 115-163; 1977.

Changes induced in the liver of female Wistar II rats by aflatoxin B_1 (AFB; 25 μg/day, 5 days/wk for 8 wk, by gastric intubation) were examined by light (LM) and electron microscopy (EM). Animals were sacrificed weekly during the first 8 wk and then at various intervals up to 66 wk. By 16 wk, only an increased number of megalocytes was detected by LM. EM revealed profound changes in the liver parenchyma. Depending on their location within the liver lobule, hepatocytes underwent two main patterns of modification. While periportal hepatocytes rapidly degenerated, more peripherally located parenchymal cells first showed a high proliferation of the endoplasmic reticulum, similar to that seen in hepatocytes engaged in drug metabolism; then they underwent degeneration in a pattern similar to that seen in the periportal cells. The endoplasmic reticulum was affected first, followed by depletion of glycogen and alteration of Golgi zones and then by damage to mitochondria and the cell membrane. Between 17 and 37 wk, LM revealed the appearance of small periportal foci of newly born hepatocytes that subsequently degenerated and a progressive disappearance of megalocytes. Sublobular changes resembling those seen previously were seen by EM. After 42 wk, LM showed a diffuse proliferation of periportal hepatocytes, which resulted in the appearance of islands of neoplastic cells. Degenerative changes in the new hepatocytes consisted either in addensation of their basophilic cytoplasm toward the periphery of the cell or in vacuolation of their cytoplasm. EM revealed changes corresponding to those observed at the cellular level. Thus, the lag time preceding the appearance of recognizable cancer is characterized by a constant spectrum of ultramicroscopic changes. Since the cells showed identical phenotypical changes after AFB_1 was discontinued, it is postulated that the cells have an endogenous mechanism for the storage and release of AFB_1. (49 refs)

78-6723 **Ultrastructure of Hepatic Neoplasia.** (Eng) Butler, W. H. (Imperial Chemical Industries, Ltd.,

Macclesfield, Cheshire, England); Jones, G. *In: Rat Hepatic Neoplasia; Workshop on Rat Liver Neoplasia held by William F. Merrell, Co. in Woods Hole, October, 1974.* William F. Merrell, Co. (Woods Hole, MA): 288 pp.; 142-179; 1978.

The ultrastructure of the hepatic tumors induced in male Porton/Wistar and Fischer rats by aflatoxin (5 ppm diet for 6-15 wk) was studied. The aflatoxin-induced tumors included trabecular and glandular carcinomas. The trabecular hepatocellular carcinomas were composed of cells retaining many of the features of normal hepatocytes. The overall structure of the liver cell plates was lost, and the vascular pole was always limited by a basement membrane. This basement membrane appeared to be associated with the endothelium or stromal cells. Although relatively normal bile canaliculi were seen, some were greatly dilated, giving rise to a tubular appearance. A continuity was seen between the trabecular and glandular tumor forms without any great difference in ultrastructure, indicating that these cells were variants of the same neoplasm. The observations suggested lack of evidence, at the ultrastructural level, for the apparent pleomorphism of cell type within the tumors. It was not possible to point to any single feature that identified malignant neoplasia. (16 refs)

78-6724 **Nickel Chloride: Kinetics of Distribution in the Rat Lung (Meeting Abstract).** (Eng) Williams, S. J. (Dept. Pharmacology and Medicine, Duke Univ. Medical Center, Durham, NC, 27710); Holden, K. M.; Menzel, D. B. *Pharmacologist* 20(3): 276; 1978. (no refs)

78-6725 **On the Possible Formation of Bis(chloromethyl) Ether from Flame Retardants.** (Eng) Loewengart, G. (Lab. Organic Chemistry and Carcinogenesis, Inst. Environmental Medicine, New York Univ. Medical Center, New York, NY); Van Duuren, B. L. *In: Prevention and Detection of Cancer. Proceedings of the Third International Symposium on Detection and Prevention of Cancer Held by the International Study Group for the Detection and Prevention of Cancer in New York, April 26 - May 1, 1976.* International Study Group for the Detection and Prevention of Cancer. (New York, NY): Vol. 2(Part 1), 2404 pp.; 1907-1912; 1978.

Bis(chloromethyl) ether (BCME) was not detected in commercial aqueous tetrakis(hydroxymethyl)phosphonium chloride (THPC, a flame retardant) by techniques that detect $\leq$ 0.1 ppm BCME, even though the soln contained 16.1% chloride ion and a large amount of CH_2O. THPC and another phosphonium flame retardant had tumor-promoting activity on mouse skin. Both chemicals reacted with guanosine to give a 2-amino substituted product that was isolated and identified. (14 refs)

78-6726 **Hamster Cell Model System for Identifying Carcinogens.** (Eng) Pienta, R. J. (In Vitro Carcinogenesis Section, Chemical Carcinogenesis Program Frederick Cancer Res. Center, Frederick, MD). *In: Carcinogens: Identification and Mechanisms of Action. Proceedings of the Thirty-First Annual Symposium on Fundamental Cancer Research Held at Houston, Texas, 1-3 March 1978.* University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, NCI, American Cancer Society (Austin, Texas). 9-10 pp.; 1978. (no refs)

78-6727 **Betel Quid Chewing and Oral Cancer: Experimental Studies.** (Eng) Ranadive, K. J. (Biology Div., Cancer Res. Inst., Bombay 400 012, India); Gothoskar, S. V. *In: Prevention and Detection of Cancer. Proceedings of the Third International Symposium on Detection and Prevention of Cancer Held by the International Study Group for Detection and Prevention of Cancer in New York, April 26 - May 1, 1976.* International Study Group for the Detection and Prevention of Cancer. (New York, NY): Vol. 2(Part 1), 2404 pp.; 1745-1766; 1978.

The ingredients of the betel quid chewed in India (tobacco extract + lime, betel nut, and betel leaf) were investigated separately and in various combinations for carcinogenicity in vivo and in vitro. The oral mucosa of 29 Wistar rats, raised on a vitamin B-deficient diet, was painted 2x/wk with acetone extract of tobacco + lime for 16-18 mo. Atypia of the oral mucosa, with massive epithelial hyperplasia, disintegration of the basement membrane, and basal cell dispersal was observed in 50% of the animals. Carcinogenesis was accelerated in golden hamsters painted on the cheek pouch and in C17 mice painted on the skin 3x/wk with a tobacco + betel nut extract compared with hamsters and mice treated with tobacco extract alone. Betel nut acted as a cocarcinogen to enhance carcinogenesis in 75% of hamsters and 33% of mice. In Swiss mice injected sc with a water extract of betel leaf and observed for life (20-24 mo), no tumors developed. In mice injected sc with a water extract of betel nut, typical transplantable fibrosarcomas developed in 24/40 mice at the injection site. The results of in vitro testing correlated well with the in vivo results. (16 refs)

78-6728 **Breast Cancer in a Patient Under Levodopa Treatment.** (Eng) Bozzetti, F. (Via G. Venezian 1, Istituto Nazionale Tumori, 20133 Milano, Italy); Galanti, E.; Costa, A. *Tumori* 64(3): 267-271; 1978.

A 62-yr-old woman developed breast cancer after 5.5 yr of continuous treatment with L-dopa [3-(3,4-dihydroxyphenyl)-L-alanine] for Parkinson's disease. The prolactin inhibition by L-dopa was verified, but the rapid growth and evolution of this tumor and comparisons with other breast cancer patients suggested that prolactin does not have an inducing or promoting effect on breast cancer. (19 refs)

78-6729 **Quantitative Histochemical and Autoradiographic Studies of Hepatocarcinogenesis**

s Fed 2-Acetylaminofluorene Followed by Phenobarbitol. g) Pugh, T. D. (Dept. Pathology, Univ. Wisconsin Sch. dicine, Madison, WI, 53706); Goldfarb, S. *Cancer Res* 12): 4450-4457; 1978.

attempt was made to characterize the hyperplastic atocellular islands that develop during chemical carcino-esis and to determine whether hepatocellular carcinomas elop from progenitor cells through a sequential process. e Buffalo rats 30 days old were fed a 30% protein diet taining 0.02% 2-acetylaminofluorene (2-AAF) for 4 wk owed by 0.05% phenobarbital in the same diet for 39 wk, mbination that induced hepatocellular neoplasms in 5/6 and 195 phenotypically altered islands. To determine relations between cell replication rates and other traits of islands, ^{3}H-thymidine-labeling indices and the activities hree enzymes were studied in serially cut cryostat sec-s. The enzymes were ATPase, glucose-6-phosphatase P), and γ-glutamyl transpeptidase (GGT). Among the nds, 89% were GGT+, 71% were ATP-, and only 35% e G6P-; those islands with variations in all three enzyme ems had significantly higher ^{3}H-thymidine-labelling in-s than islands with only one or two variations. The acqui-n of GGTase activity was the best marker for hyperplas-slands, although decreased G6P activity characterized a ll subpopulation of islands with higher rates of cell re-ation. It is concluded that the increasing phenotypic ersity of islands associated with increasing rates of cell ication supports the clonal hypothesis of carcinogenesis. refs)

6730 **Mechanism of In Vitro Mutagenic Activation and Covalent Binding of N-Hydroxy-2-tylaminofluorene in Isolated Liver Cell Nuclei from and Mouse.** (Eng) Sakai, S. (Biochemical Pharma-ogy Section, Lab. Chemical Pharmacology, Develop-ntal Therapeutics Program, Div. Cancer Treatment, I, NIH, Bethesda, MD, 20014); Reinhold, C. E.; th, P. J.; Thorgeirsson, S. S. *Cancer Res* 38(7): 8-2067; 1978.

in vitro mutagenic activation (MA) of ydroxy-2-acetylaminofluorene (N-OH-AAF) in *Sal-nella typhimurium* strain TA1538 by isolated rat and use liver cell nuclei and the in vitro covalent binding of OH-AAF to nuclear nucleic acids and proteins were stud-Mutagenic MA of N-OH-AAF and 2-acetylaminofluo-by liver cell nuclei was observed. The MA of OH-AAF by mouse nuclei was 6-7 times greater than that the rat nuclei (2,300 vs 350 revertants/10 μg OH-AAF). The mutagenicity of N-OH-AAF was in-sed twofold when NADPH was included with the nuclei; increase was inhibited by α-naphthoflavone. The carbox-erase:amidase inhibitor paraoxon (10^{-5} M) completely ibited the MA of N-OH-AAF in the 100,000 *g* super-ant from rat liver (RLS), whereas 50% inhibition N-OH-AAF mutagenesis was observed when adeno-3′-phosphate 5′-phosphosulfate was added to the RLS. The addition of RLS to mouse liver nuclei resulted in a decreased mutagenicity of N-OH-AAF that could be further inhibited by paraoxon. On the other hand, the addition of this supernatant to rat liver nuclei resulted in an increase in N-OH-AAF mutagenicity that was insensitive to inhibition by paraoxon. Vitamin E and butylated hydroxytoluene (10^{-2} M) inhibited the MA of N-OH-AAF by 20%-30% in the mouse nuclear preparation, whereas vitamin C at the same concentration increased N-OH-AAF mutagenesis two- to threefold. Addition of cysteamine and methionine (10^{-2} M) to the mouse nuclear preparation resulted in 60% and 30% inhibition, respectively, of N-OH-AAF mutagenesis. The first step in the in vitro MA of N-OH-AAF by isolated rat and mouse liver cell nuclei and/or RLS and the in vitro covalent binding of N-OH-AAF to nuclear nucleic acids and protein occur primarily via deacetylation of the carcinogen by either the membrane-bound amidase or the N,O-acyltransferase in the supernatant fraction. (48 refs)

78-6731 **Metabolism of 2-Acetylaminofluorene in Primary Cultures of Rat Hepatocytes (Meeting Abstract).** (Eng) Spilman, S. D. (Dept. Environmental Toxicology, Univ. California, Davis, CA, 95616); Byard, J. L. *Pharmacologist* 20(3): 175; 1978. (1 ref)

78-6732 **Influence of Chemical Carcinogens on the Physiological Effects of Adrenomimetics.** (Rus) Gurkalo, V. K. (Lab. Chemical Carcinogens, N. N. Petrov Res. Inst. Oncology, Leningrad, USSR); Pliss, G. B. *Vopr Onkol* 24(4): 49-53; 1978.

The carcinogen-induced activation of α- and β-adrenoreceptors was studied in isolated rat and guinea pig atria. Exposure of the atria to the hepatocarcinogens 2-acetylaminofluorene (AAF: 1 μg/ml) or diethylnitrosamine (DENA: 0.01 μg/ml) increased the rate and amplitude of spontaneous contractions. At large concentrations, AAF and DENA (10-50 and 1-10 μ/ml, respectively) inhibited the spontaneous contractions completely. AAF selectively inhibited the inotropic effect of norepinephrine in rat atria, but not in guinea pig atria. DENA had a similar effect on rat and guinea pig atria. In rat atria, sensitivity to noradrenaline decreased with increase in AAF concentrations. (15 refs)

78-6733 **Nitrates and Nitrites in the Human Diet (Letter to Editor).** (Eng) Hartman, P. E. (Mergenthaler Lab. Biology, Johns Hopkins Univ., Baltimore, MD, 21218). *Science* 202(4365): 260; 1978.

Of the gastric nitrite in healthy individuals, 28% is probably derived from cured meats as opposed to the < 20% quoted previously. Cured meats are suspect teratogens, and strong correlations have been demonstrated between nitrite ingestion, gastric nitrite, and stomach cancer. Heavy fertilization

may be increasing the nitrate content of spinach and tomatoes. (10 refs)

78-6734 **Chronic Inhalation Toxicity of 2-Nitropropane in Rats (Meeting Abstract).** (Eng) Griffin, T. B. (No affiliation given); Benitz, K. F.; Coulston, F.; Rosenblum, I. *Pharmacologist* 20(3): 145; 1978. (no refs)

78-6735 **Studies on the Immunological Response in Rats with Experimental Urinary Bladder Carcinoma.** (Jpn) Nishijima, T. (Dept. Urology, Osaka City Univ. Medical Sch., Osaka, Japan). *Jpn J Urol* 69(8): 1044-1054; 1978.

Experimental bladder tumors were induced in Wister rats by po administration of 0.025% N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN), and changes in the bladder histopathology and in the mitogen response of lymphocytes with time were investigated. There were no significant differences in body wt between the experimental and control groups. However, there was a significant increase in bladder wt and a significant decrease in thymus wt ($p < 0.01$) in the experimental group. At 12 wk after BBN administration, hyperplasia began to develop in the bladder mucous epithelium; there was gradual growth in a papillary form and, after 24 wk, transitional cell carcinomas were found in all rats. The stimulation index values of the lymphocytes from the cervical and mesenteric lymph nodes began to decrease significantly ($p < 0.005$) from the time hematuria was observed macroscopically (about 21 wk after BBN treatment), but there were no significant differences between the responses to phytohemagglutinin (PHA) and concanavalin A (Con A). The SI values of the thymic lymphocytes decreased significantly ($p < 0.01$) from the time hyperplasia was found in the bladder mucous membrane (about 15 wk), before the significant reduction in the mitogen responses of lymph node lymphocytes. The decrease was much greater with Con A than with PHA stimulation. (55 refs)

78-6736 **Malignancies Associated with Immunosuppressive or Cytotoxic Therapy.** (Eng) Penn, I. (Dept. Surgery, Univ. Colorado Medical Center, 4200 E. Ninth Ave., Denver, CO, 80220). *Surgery* 83(5): 492-502; 1978.

The increased risk of malignancy in five groups of patients receiving immunosuppressive or cytotoxic therapy is discussed. There is a 36% incidence of neoplasia in transplant recipients who received organs from donors with cancer. Transplant patients have a 6% risk of developing de novo tumors at some time after transplantation; this frequency is 100 times greater than that for the general population in the same age range. Patients who undergo transplantation as treatment for malignancies have variable recurrence rates: 62.5% following liver replacement for hepatic malignancies, and 31% after bone marrow grafting for acute leukemia. The treatment of renal malignancies by kidney transplantatio has a 53% recurrence rate if the interval between treatmer of the cancer and transplantation is ≤1 yr; no recurrence have been noted with longer waiting periods. Neoplasms hav also occurred in nontransplant patients treated with im munosuppressive agents. Cancer patients treated wit chemotherapy may subsequently develop second or third tu mors. A statistically significant increase in the incidence c acute myeloid leukemia has been noted in patients given cyto toxic therapy for multiple myeloma, Hodgkin's disease, an ovarian cancer. Thus, immunosuppressive and cancer chemo therapeutic agents should be used with caution, and th long-term use of immunosuppressive agents in nontransplan patients with nonmalignant disease should be restricted t those in whom all other forms of therapy have failed. (10 refs)

78-6737 **Depression by Ethionine of Phosphorylatin Oxidation in Hepatic Mitochondria.** (Eng) Hi gins, E. S. (Dept. Biochemistry, Medical Coll. Virginia, Vi ginia Commonwealth Univ., Richmond, VA, 23298); Frien W. H.; Rogers, K. S. *Experientia* 34(5): 578-579; 1978.

The immediate effect of ethionine on the ATP generatin capacity of male Sprague-Dawley rat hepatic mitochondr was investigated in vivo and in vitro. The induction of hepat steatosis and the suppression of hepatic ATP levels, prote synthesis, and gluconeogenesis subsequent to ethionine a ministration may be consequences of its interference with t mitochondrial phosphorylation of ADP. The mitochondri dysfunction is not a direct action of ethionine on the c ganelle. (19 refs)

78-6738 **Saccharin, Cancer, and Calories (2 Letters Editor).** (Eng) Campbell, T. C. (Federati American Societies Experimental Biology, Bethesda, M 20014). *Science* 202(4365): 260-262; 1978.

In comments on a report based on estimates of the Food a Drug Administration (FDA) linking bladder cancer to sa charin ingestion, species differences in response to carcin gens are discussed. The responses can vary by three or fo orders of magnitude. The assumption that noncaloric swe ners reduce calorie consumption is also questioned. In rep the FDA's risk estimate is also questioned and several exa ples of how uses of saccharin do decrease calorie intake a cited. (6 refs)

78-6739 **Histological Conformity of Implantation T mors Produced by Kidney Cell Lines Deriv from Dimethylnitrosamine-treated Rats with Dimethyl trosamine-induced Renal Mesenchymal Tumors.** (En Hard, G. C. (Fels Res. Inst., Temple Univ. Sch. Medici

adelphia, PA, 19140). *Cancer Res* 38(7): 1974-1978;

histology of five implantation tumors induced in Wistar by the deposition of cultured cell lines derived from ethylnitrosamine (DMN)-treated rats is described and pared with the morphology of the predominant kidney lasm induced in vivo by a single high dose (60 mg/kg) MN. The cell lines leading to growth upon implantation long-established, continuously growing cultures ob- d from either a DMN-induced renal mesenchymal tu- or from rats treated shortly (2 hr) before with a carcino- c dose (60 mg/kg) of DMN. The latter cultures expressed phological transformation at subcultures 5 or 6. All of mplantation tumors were of the mesenchymal type, com- ng a range of cell forms that included fibroblastlike spin- ells, smooth muscle fibers, and giant cells, which resem- common aspects of the parent mesenchymal tumors ced in the rat kidney by DMN. The deposition of cells renally illustrated the survival of remnants of preexisting rons as epithelial profiles scattered through the prolife- g malignant tissue, a feature most characteristic of the nt tumor. The results confirmed the malignant nature of various cell lines tested, and they were consistent with premise that the in vivo-in vitro system selected cells in re that represented the same target population from h the renal mesenchymal tumors were derived in vivo. refs)

740 **Macroautoradiographic Study of the Distribution of ^{14}C-Dimethylnitrosamine in Mice and ses.** (Eng) Takahashi, G. (Dept. Pathology, Chest Dis- Res. Inst., Kyoto Univ., Kyoto, Japan). *Bull Chest Dis Inst Kyoto Univ* 11(1/2): 81-85; 1978.

Dimethylnitrosamine (DMN: 5 μCi) was administered r iv to pregnant ICR mice on day 18 of gestation, and distribution of radioactivity in the mice and their fetuses determined by macroautoradiography of serial saggital ons. Intense radioactivity was noted 30 min after iv ad- istration in the liver, kidneys, bone marrow, glandular es, skin appendages, pancreas, mucous membranes of the l cavity, intestines, and glandular stomach. This pattern maintained for up to 2 hr. The distribution of radioactivi- as similar 30 min after po administration of the carcino- with intense labeling noted primarily in the liver, kidney, n and pancreas. Labeled DMN or its metabolites passed ugh the placenta and were evenly distributed in fetal liv- ntestines, bone marrow, and thymus. Because the in vivo inogenic activity of DEN is due to its demethylated abolites, a comparison of radioactive label concentration tissue susceptibility to DMN has limited value. (18 refs)

741 **Occurrence of Methylguanidine and Agmatine in Foods.** (Eng) Kawabata, T. (Dept. Biomedical Res. Food, Natl. Inst. Health, Tokyo, Japan); Ohshima, H.; Ino, M. *IARC Sci Publ* (19): 415-423; 1978.

Various fresh and processed foods were analyzed by a new series of methods for the presence of two mutagenic guanidino compounds, nitrosated methylguanidine (MG) and nitrosated agmatine (AG). The methods consisted of trichloroacetic acid extraction, separation of the extract into fractions by ion-exchange chromatography, colorimetric analysis of each fraction, and identification of the compounds by gas chromatography-mass spectrometry. Sixty-five fresh and smoked or cured fish and meat samples were analyzed. MG was not detected or was negligible in all samples except in three smoke-dried fish products: skipjack (178 mg/kg), chubmackerel-horse mackerel mixture (56 mg/kg), and sardines (37.8 mg/kg). These seasoning products, which are declining in use, are only used in small quantities and cannot be related to the high gastric cancer incidence in Japan. Relatively high AG levels (mg/kg) were found in fresh abalone and top shell (40-240) and in some processed fish, including fresh Alaskan pollack roe (72.5), salt-dried herring (217), salted squid (650), dried filefish (112), and smoked scallops (44.8). It is suggested that the high MG levels found in earlier food studies were due to the use of metallic salts, which catalyzed the oxidation of creatine or creatinine to give MG as an artifact. (16 refs)

78-6742 **Ornithine Decarboxylase and Polyamines: Relationship to N-Nitrosamine Carcinogenesis.** (Eng) Farwell, D. C. (Univ. New Hampshire, Durham, NH). *Diss Abstr Int B* 39(2): 706; 1978. (no refs)

78-6743 **Effects of Carcinogenic and Non-carcinogenic Chemicals on Plasma Esterases in BALB/c Mice.** (Eng) Tyndall, R. L. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830); Clapp, N. K.; Davidson, K. A.; Colyer, S. P.; Burtis, C. A. *Chem Biol Interact* 23(2): 159-169; 1978.

Esterase profiles of plasma from female BALB/c mice treated with a variety of carcinogenic, weakly carcinogenic, and non-carcinogenic chemicals were analyzed to determine whether these chemicals produce esterase alterations similar to those of diethylnitrosamine and butylated hydroxytoluene and if such alterations are more sensitive indicators of these chemicals than standard clinical chemistry tests. Mice that received diethylnitrosamine (40 mg/liter), dinitrosopiperazine (100 mg/liter), dipropylnitrosamine (100 mg/liter), dimethylhydrazine (50, 100, or 800 mg/liter), urethane (10,000 mg/liter), or dimethyldinitrosopiperazine (50, 100, or 800 mg/liter) in their drinking water for 7 days had similarly altered plasma esterase profiles. These consisted of increased activity in four esterase bands. The increased activity persisted in some bands after cessation of carcinogen exposure. Exposure to high concentrations of the weakly carcinogenic or

noncarcinogenic compounds nitrosohydroxyproline (100 mg/liter), nitrosomethoxymethylamine (100 mg/liter), 1-nitroso-4-methylpiperazine (100 mg/liter), nitroso-2,6-dimethylpiperidine (100 mg/liter), or ethyl methanesulfonate (200 mg/liter) caused no obvious plasma esterase alterations. Carbon tetrachloride ingestion (800 mg/liter) increased the activity in one esterase band and decreased the activity in a second band. Analysis of serum from test mice for levels of SGOT, alkaline phosphatase, lactate dehydrogenase-lactate substrate, and *D*-γ-glutamyl transpeptidase did not differentiate between mice treated with selected carcinogens and those treated with noncarcinogens and/or carbon tetrachloride. (33 refs)

78-6744 **Low Level of Unscheduled [^{3}H]Thymidine Incorporation into Hyperplastic Nodule and Hepatoma Cells after Exposure to Dimethylnitrosamine In Vivo.** (Eng) Ogawa, K. (Dept. Pathology, Sapporo Medical Coll., S.1, W.17, Chuo-ku, Sapporo 060, Japan); Enomoto, K.; Yoshida, Y.; Onoe, T. *Chem Biol Interact* 23(2): 259-262; 1978.

In order to investigate why hyperplastic liver nodules that arise prior to and with hepatoma development are resistant to the cytotoxic and growth inhibitory effects of various hepatocarcinogens, the effect of in vivo exposure to dimethylnitrosamine (DMN) was investigated in male Wistar rats bearing these lesions. The lesions had been induced by continuous administration of diethylnitrosamine in the drinking water (6 mg/kg/day) for 4 wk or by 3′-methyl-4-(dimethylamino)azobenzene in the diet (0.06%) for 12 wk. They were then maintained carcinogen-free for 28 and 8 wk, respectively. Rats were treated with 30 mg/kg DMN ip; 4.5 hr later, chilled Eagle's minimal essential medium was perfused through the portal vein. DNA synthesis was studied in excised livers that had been incubated with ^{3}H-thymidine. Without prior DMN treatment, fairly large numbers of grains were localized on the cytoplasm and nuclei of both normal liver and hyperplastic nodules, probably due to incorporation of tritiated moieties from catabolized ^{3}H-thymidine into macromolecules other than nuclear DNA. After DMN treatment, normal liver cells showed increased number of grains on the nuclei. The two hyperplastic nodules and one hepatoma examined showed no increase in ^{3}H-thymidine incorporation into nuclei after DMN treatment, whereas surrounding liver showed a distinct increase of grains on the nuclei, as did normal liver cells. These results show that in vivo DMN treatment decreases unscheduled DNA synthesis in hyperplastic nodules and hepatomas, suggesting that these lesions may be capable of escaping from carcinogen-induced DNA damage in vivo. (16 refs)

78-6745 **Transformation of Mouse Mammary Glands in Whole Organ Culture by Carcinogenic Aromatic Amines and Amides (Meeting Abstract).** (Eng) Tonelli, Q. J. (Inst. for Cancer Res., Fox Chase Cancer Center, Philadelphia, PA, 19111); Sorof, S. *J Cell Biol* 79(2, part 2): 73a; 1978. (no refs)

78-6746 **Deuterium Isotope Effect on Rat Liver DNA Damage In Vivo by Dimethylnitrosamine.** (Eng) Oshiro, Y. (Searle Labs., Box 5110, Chicago, IL, 60680); Sarma, D. S.; Zielinski, W. L. *Chem Biol Interact* 23(2): 263-266; 1978.

The deuterated analog (DMN-d_6) of dimethylnitrosamine (DMN) proved to be less effective than DMN in inducing in vivo DNA damage after ip administration to rats in doses from 0.37 to 3.20 mg/kg. Hepatic cell DNA damage after labeling with ^{3}H-thymidine was measured by alkaline sucrose gradient sedimentation. At all dose levels, DMN-d_6 treatment resulted in a greater percentage of labeled DNA sedimenting at a mol wt $> 13 \times 10^6$ than DMN treatment. The distribution of slower-sedimenting DNA was always lower after DMN-d_6 than after DMN treatment. The sedimentation as heavy DNA, compared with control DNA, was taken to be a direct indication of DNA damage. The differences in the ability of DMN-d_6 and DMN to cause in vivo DNA damage were apparent at 10 min after administration, but they became less apparent with longer periods between treatment and sacrifice. Because DMN has to be metabolized to chemically modify DNA, it is hypothesized that the differential mutagenic capability of DMN-d_6 is due to the slower activation of this perdeuterated analog. (16 refs)

78-6747 **Blood, Tissue and Subcellular Distribution of Radioactivity Following Administration of ^{14}C-Dimethylnitrosamine (DMN) or ^{14}C-Dimethylamine (DMA) in Guinea Pigs (Meeting Abstract).** (Eng) Chaudhari A. (Pharmacology Dept., Wayne State Univ., Detroit, MI 48202); Dutta, S. *Pharmacologist* 20(3): 175; 1978. (no refs)

78-6748 **The Significance of Some Modifying Factors During Transplacental Blastomogenesis by Ethylnitrosourea in Rabbits.** (Eng) Dimant, I. N. (Uzbek Res. Inst. Oncology and Radiology, 700 000 Tashkent, USSR); Beniashvili, D. Sh. *Neoplasma* 25(4): 453-460; 1978.

The effects of three treatments, organospecific immunity, chronic irritation of the peripheral nerve, and methylnitrosourea (MNU), on the development of ethylnitrosourea (ENU)-induced transplacental blastomogenesis were studied in chinchilla rabbits. Groups of 36 weaned rabbits, whose mothers had been treated during pregnancy with ENU, either served as controls or underwent one of the three treatments. The immunized animals (Group 1) were treated three times with antigens from the homologous tissue of the sciatic nerve

Group 2, the left sciatic nerve was chronically irritated by plying a nylon squeezing free ligature, the ends of which ere attached to the femoral muscle. Contraction of this mus- e produced irritation of the nerve. The MNU-treated ani- als (Group 3) received a weekly iv dose of 10 mg/kg for 5 mo. All animals were observed for 4 yr. The total number tumors developing in survivors, 27 Group 1, 26 Group 2, Group 3, and 36 control rabbits, was 17, 12, 4, and 10, spectively. The total number of peripheral nervous system mors in the respective groups was 8, 7, 2, and 4. It appears at the first two treatments increased the frequency of tumor evelopment, particularly that of peripheral nerve tumors. INU apparently inhibited ENU-induced tumorigenesis. (25 fs)

8-6749 **Studies of Experimental Brain Tumorigenesis Induced by Transplacental Administration of thylnitrosourea in Rats.** (Jpn) Inui, S. (Second Dept. Surg- y, Nara Medical Univ., Nara, Japan). *J Nara Med Assoc* (1): 288-306; 1978.

Vistar rats were given a single transplacental dose of ethylni- osourea (ENU: 10-75 mg/kg), 4-hydroxyaminoquinoline -oxide (4-HAQO: 7 mg/kg), or N-bis(2-hydroxypropyl)ni- osamine (DHPN: 2,000 mg/kg) on gestation days 18 or 20, nd DNA synthesis and histopathological changes in the fetal t brain were analyzed. Four hours after administration on ay 18, ENU, 4-HAQO, and DHPN inhibited DNA synthe- s by 87.7%, 85.6%, and 87.3%, respectively, with the inhi- ition due to ENU being dose-dependent. In ENU- and -HAQO-treated rats, the inhibition persisted for 48 hr, fol- owed by a stimulation of synthesis at 72 hr after administra- on. Brain tumors were induced by ENU but not by -HAQO and DHPN. The incidence in males and females anged from 36.4% to 66.7% at 23 wk and from 90.3% to 00% at 30 wk. In order of incidence, the tumors were oligo- endrogliomas, astrocytomas, mixed gliomas, anaplastic gli- mas, medulloblastomas, and trigeminal neurinomas. Atypi- al cell foci were observed as early as 10 wk, and the incidence f these foci was higher than that of the tumors at 23 wk and ower at 30 wk. The labeling index of the oligodendrogliomas, strocytomas, anaplastic gliomas, neurinomas, and atypical ell foci was 1.92, 3.16, 7.52, 3.49, and 0.075, respectively. The atypical cell foci may represent preneoplastic lesions. (41 efs)

78-6750 **Influence of Repeated Liver Regeneration on Hepatic Carcinogenesis by Diethylnitrosamine n Mice.** (Eng) Pound, A. W. (Dept. Pathology, Univ. Queensland, Brisbane, Australia); McGuire, L. J. *Br J Cancer* 7(4): 595-602; 1978.

The effect of repeated doses of CCl_4 ip at 5-wk intervals on he tumorigenic response of diethylnitrosamine (DEN)-treat- d random-bred male Quackenbush mice was determined. The mice were divided into six groups: 1 (a), 0.25 ml/kg CCl_4 ip; (b), 24 hr later, 80 mg/kg DEN ip and, 5 wk later, repeated doses of CCl_4; 2, regimen 1b; 3, regimen 1a + DEN; 4, DEN; 5, repeated CCl_4; 6, regimen 1a. No tumors were noted in mice given single or multiple injections of CCl_4. DEN + repeated CCl_4 injections increased the tumor yield in the liver over that occurring in animals treated with DEN alone. A single hepatonecrotic dose of CCl_4 24 hr before DEN treatment also increased the number of tumors produced. The effects of the pre-DEN CCl_4 dose and the post-DEN CCl_4 doses were additive and were therefore independent of each other. The neoplasms produced were hepatocellular tumors and cholangiomas. Kidney tumors (papillary adenomas and adenocarcinomas) were also noted in the CCl_4 + DEN-treated mice. These findings indicate that the liver in the regenerative phase after a hepatonecrotic CCl_4 dose is more susceptible than normal liver to the initiating action of DEN and that repeated doses of CCl_4 after DEN provide a promoting stimulus. (18 refs)

78-6751 **Effects of the Carcinogen, N-Methyl-N′-Nitro-N-Nitroguanidine (MNNG), on Differentiation of Human Prostate Epithelium in Organ Culture (Meeting Abstract).** (Eng) Sanefuji, H. (Dept. Pathology, Univ. Maryland Sch. Medicine, Baltimore, MD); Heatfield, B. M.; Trump, B. F. *J Cell Biol* 79(2, part 2): 71a; 1978. (no refs)

78-6752 **Binding of 1-Methyl-1-nitrosourea (MNU) and 1-Methyl-3-nitro-1-nitrosoguanidine (MNNG) to L1210 Cell Histones (Meeting Abstract).** (Eng) Pinsky, S. D. (V. Lombardi Cancer Res. Center, Georgetown Univ., Washington, DC); Tew, K. D.; Woolley, P. V. *J Cell Biol* 79(2, part 2): 113a; 1978. (no refs)

78-6753 **Mycosis Fungoides, Nitrogen Mustard and Skin Cancer.** (Eng) Du Vivier, A. (St. Mary's Hosp., London W2, England); Vonderheid, E. C.; Van Scott, E. J.; Urbach, F. *Br J Dermatol* 99(1): 61-63; 1978.

The development of epithelial malignancies prior to or after treatment with topically applied nitrogen mustard (mechlorethamine, HN_2) was determined in 202 patients (135 men, 67 women) with mycosis fungoides and its Sezary variant. The records of the patients, who had been followed for up to 9 yr, were reviewed. Epithelial cancers developed in 24 patients, 3 of whom were excluded from further study because of previous treatment with arsenic. The remaining 21 patients (12 men, 9 women) had a mean age at onset of lesions of 64 yr. The mean time between initiation of HN_2 therapy and detection of epithelial neoplasms other than actinic keratoses was 4.0 yr. Of eight patients who had lesions removed prior to HN_2 therapy (Group I), five developed additional lesions after HN_2 treatment [4 squamous cell carcinomas (SCC), 4

keratoacanthomas, and 1 basal cell carcinoma]. Three of these patients had multiple tumors. The other 13 patients (Group II), who had no evidence of epithelial lesions initially, subsequently developed actinic keratoses (4 patients) and 7 SCC, 3 keratoacanthomas, and 2 basal cell carcinomas (9 patients, 3 of whom developed multiple tumors). Two of the SCC were found in locations protected from solar radiation, which offers convincing evidence that topically applied HN_2 is a carcinogen or cocarcinogen. These lesions, which appeared 6-7 yr after the start of treatment, corresponded to the use of approx 14 g HN_2/4 yr (SCC on scrotum) and 16 g/7 yr (SCC on buttock). (7 refs.)

78-6754 **In Vivo Synthesis of 1-Naphthyl N-Methylnitrosocarbamate (Nitrosocarbaryl) in the Rat and Guinea Pig (Meeting Abstract).** (Eng) Rickard, R. W. (Graduate Center Toxicology, Univ. Kentucky, Lexington, KY, 40506); Dorough, H. W. *Pharmacologist* 20(3): 146; 1978. (no refs)

78-6755 **Inhibition of the Alkylation of Nucleic Acids and of the Metabolism of 1,2-Dimethylhydrazine by Aminoacetonitrile.** (Eng) Pegg, A. E. (Dept. Physiology, Milton S. Hershey Medical Center, Pennsylvania State Univ., Hershey, PA, 17033). *Chem Biol Interact* 23(2): 273-279; 1978.

Administration of aminoacetonitrile (AAN) ip to female Sprague-Dawley rats before ip injection of ^{14}C-1,2-dimethylhydrazine (DMH) altered the latter's metabolism to $^{14}CO_2$ and ^{14}C-azomethane. The amount of $^{14}CO_2$ expired by treated rats was determined by drawing air through their cages, collecting it in gas-filled wash bottles, and measuring the radioactivity present in the bottles. When 100 mg/kg AAN was administered before 2 mg/kg ^{14}C-DMH, CO_2 production 8 hr later was reduced from 28% to 4%, and azomethane increased from 1.3% to approx 50% of the administered DMH dose. Results were similar when the ^{14}C-DMH dose was reduced to 0.5 mg/kg. When ^{14}C-DMH dose was increased to 50 or 200 mg/kg, azomethane expiration rose to 33% and 41% of the administered dose, respectively, and $^{14}CO_2$ exhalation dropped to 11% and 6%. Alkylation of rat DNA at the 7-methylguanine position after administration of 2 mg/kg DMH was inhibited 95% in the liver, 89% in kidney, and 57% in colon by pretreatment with 100 mg/kg AAN. O^6-methylguanine production was inhibited to a similar extent. The difference in the degree of inhibition of colon DNA suggests that at least one critical step in the conversion of DMH to a methylating agent for the colon occurs outside the liver. (26 refs)

78-6756 **Chemically Induced Ganglioglomas in the Opossum (*Didelphis virginiana Kerr*) (Meeting Abstract).** (Eng) Jurgelski, W. (Natl. Inst. Environmen Health Sciences, Research Triangle Park, NC); Hudson, M.; Henry, J. M.; Falk, H. L. *J Neuropathol Exp Neu* 37(5): 638; 1978. (no refs)

78-6757 **Molecular Basis for the Neoplastic Transform tion of Neuroectodermal Cells by N-N trosoureas.** (Eng) Chang, M. J. (Ohio State Univ., Columb OH, 43210). *Diss Abstr Int B* 39(2): 701; 1978. (no refs)

78-6758 **Long-Term Effects of Phenobarbitone-Na Male Fischer Rats.** (Eng) Butler, W. H. (Saf Medicines Dept., Pharmaceuticals Div., ICI, Ltd., Meresi Alderley Park, Macclesfield, Cheshire, SK10 4TG, Englan *Br J Cancer* 37(3): 418-423; 1978.

Preliminary results are given of an experiment in which male inbred Fischer rats were fed sodium phenobarbitone a level of 500 ppm in the diet for 1 wk followed by 1,000 pp for 103 wk. Of 33 rats surviving ≥80 wk, 11 had small f of nodular hyperplasia; however, 1 killed at 102 wk had larger lesion (0.75 cm) with no evidence of local invasion metastases. All livers had evidence of parenchymal cell da age. No nodular hyperplasia was found in the controls. It concluded that this compound is not carcinogenic in Fisch rats. (9 refs)

78-6759 **Evidence from *Haemophilus influenzae* for E ror-Prone Repair Systems with Different Mut gen Specificities (Meeting Abstract).** (Eng) Kimball, R. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 3783 Boling, M. E.; Perdue, S. W. *Mutat Res* 53(2): 209-210; 197 (no refs)

78-6760 **Effect of Pyrazole on Tumor Induction by M thylazoxymethanol (MAM) Acetate: Relatio ship to Metabolism of MAM (Meeting Abstract).** (Eng) Z deck, M. S. (Sloan-Kettering Inst., New York, NY, 1002 Tan, Q. H. *Pharmacologist* 20(3): 174; 1978. (2 refs)

78-6761 **Relative Sensitivities of Forward and Rever Mutation Assays in *Salmonella typhimuriu*** (Eng) Skopek, T. R. (Toxicology Group, Dept. Nutrition a Food Science, Massachusetts Inst. Technology, Cambridg MA, 02139); Liber, H. L.; Kaden, D. A.; Thilly, W. G. *Pr Natl Acad Sci USA* 75(9): 4465-4469; 1978.

The relative sensitivities of the forward and reverse mutati assays in *Salmonella typhimurium* were compared with t

of 16 mutagens of both base-substitution and frameshift es. Forward mutation of 8-azaguanine resistance was sured with strains TM35 and TM677; reverse mutation istidine prototrophy was measured with the Ames tester ns TA1535, TA1537, TA1538, TA98, and TA100. The n spontaneous revertant mutant fractions ranged from x 10^{-8} (TA1538) to 22 x 10^{-8} (TA100). The mean spon- ous forward mutant fraction was 1.7 x 10^{-5} for TM35 and x 10^{-5} for TM677. The two approaches were found to be sensitive for all 16 mutagens; ie, induction of significant ation occurred at similar concentrations in the forward ation assay and in the most sensitive of the five Ames er strains. The combined assays provide an improved ns of quantitating chemomutagenic potential. (9 refs)

6762 **Mutagenic Properties of Quinoline.** (Eng) Hollstein, M. C. (Univ. California, Berkeley, CA). *Abstr Int B* 39(2): 673; 1978. (no refs)

6763 **Macroautoradiographic Assays of ^{14}C-Labeled 4-Nitroquinoline 1-Oxide in Adult and Fetal e.** (Eng) Takahashi, G. (Dept. Pathology, Chest Disease . Inst., Kyoto Univ., Kyoto, Japan); Kinoshita, K.; uhira, K. *Bull Chest Dis Res Inst Kyoto Univ* 11(1/2): 90; 1978.

distribution of ^{14}C-labeled 4-nitroquinoline 1-oxide (QO) and its metabolites in adult, pregnant, and fetal mice studied by macroautoradiography. 4NQO (7.5 μCi, 230 was administered iv to pregnant mice on days 16 or 19 gestation or injected iv or sc in young adult mice. All mals were killed 1, 3, 5, or 24 hr later. Concentrations of ioactive substances were nearly equal in fetal tissue, pla- ta, and maternal blood 1 hr after iv administration. Al- ugh fetal organ distribution of radioactivity was uniform day 16 of gestation, the 19 kidneys, urinary bladder, and estinal tract were intensely labeled on day 19. In normal lt mice, radioactivity 1 hr after iv 4NQO administration centrated most intensely in the gallbladder, small intes- e, lungs, kidneys, and bladder. There was moderate activi- in the liver, heart, muscle, salivary glands, and blood. dioactive substances tended to deposit at the injection site r sc administration, but they also accumulated in the gall- dder, intestine, bladder, and kidneys. No direct relation- p between organ susceptibility to 4NQO and the concen- tion of radioactivity was observed. (10 refs)

-6764 **Effect of a Single Injection of 4-Dimethylaminoazobenzene on Some Properties of t Liver Cell Mitochondria.** (Rus) Medvedeva, N. D. (Lab. mor Cytology, Inst. Cytology, Acad. Sciences, USSR, ningrad, USSR); Khodosova, I. A. *Tsitologiia* 20(10): 92-1196; 1978.

The effects of a single ip injection (250 mg/kg) of the hepatocarcinogen 4-dimethylaminoazobenzene (DAB) and its noncarcinogenic analog, 4-diethylaminoazobenzene (DEAB), on rat liver mitochondria were studied. DAB had no noticeable effect on mitochondrial and cytoplasmic malate dehydrogenase activity. Both substances caused a significant inhibition of mitochondrial cytochrome oxidase activity on the first day (to 51.3% by DAB and to 42.2% by DEAB), but there was no significant difference between the effects of the two substances. This activity returned to normal levels on day 4. The swelling-contraction properties of isolated mitochondria were reduced in the presence of succinate and ATP, even 18 days after a single DAB injection. However, DAB had no effect on mitochondria from the kidney, which is not its target organ. The changes are interpreted as the result of the action of the carcinogen on the mitochondrial membranes. (15 refs)

78-6765 **Need for Ascertaining Environmental History in Leukemia and Malformations in Children.** (Swe) Haglund, B. (Halsovardsenheten, Bassjukhuset, S-541 00 Skovde, Sweden); Kjellman, B. *Lakartidningen* 75(39): 3436-3437; 1978.

The necessity and importance of ascertaining the environmental history of children with leukemia and malformations are illustrated by case reports. A woman exposed occupationally to xylene vapors and freon in an unventilated room gave birth to a boy who was subsequently exposed to styrene, acetone, and xylene while his father was building a plastic boat. The boy developed acute lymphocytic leukemia at age 2 yr. One of the mother's colleagues gave birth to a girl with bilateral talipes equinovarus, the other to a girl with gastroschisis and exstrophy of the bladder. A 10-yr-old boy developed acute leukemia a few months after he was exposed to solvents, mainly trichloroethylene, while building plastic models. A 6-yr-old girl exposed frequently to solvents and living in a house in which the radioactivity level was about four times higher than the background level developed leukemia. The girl's grandfather, who had been occupationally exposed to solvents as an automobile mechanic, died from chronic lymphocytic leukemia. (13 refs)

78-6766 **A Study of Cyclic Nucleotide Metabolism and the Histology of Rat Liver During 3′-Methyl-4-dimethylaminoazobenzene Carcinogenesis. II. Cyclic AMP Metabolism.** (Eng) Boyd, H. (Dept. Pharmacology, Univ. Miami Sch. Medicine, P. O. Box 520875, Miami, FL, 33152); McAfee, D. A.; Rubin, J. J. *Tissue Cell* 10(3): 477-494; 1978.

Adenyl cyclase (AC) activity and cyclic AMP (cAMP) metabolism were studied in Sprague-Dawley rat livers undergoing carcinogenesis induced by dietary 3′-methyl-4-dimethylaminoazobenzene (0.06%). All treated rats developed

cholangiocarcinomas by 10 wk. AC activity, assessed from the crude membrane fraction, increased slowly for 3 wk and then rose to a peak of 565% of control values at 9 wk post-treatment. Stimulation with isoproterenol increased this peak to 640%; guanylylimidodiphosphate (Gpp(NH)p) and sodium fluoride also stimulated AC activity, but glucagon had no significant effect. Enzyme activity was higher in tumor-bearing animals than in controls, and it was higher in areas of tumor involvement than in noninvolved tissue from the same animal. The patterns of responsiveness to the AC stimulators indicated that there were differences not only in the onset of hormonal stimulation of the enzyme and the transduction mechanism, but also a difference in the time at which these changes were no longer seen. The former preceded tumor induction; the latter accompanied tumor induction and persisted in tumors and uninvolved tissue. Cyclic AMP levels in treated animals showed a consistent and significant elevation (120%-250%) after wk 3, but they were strikingly increased in tumor tissue (up to 1500%). Particulate phosphodiesterase activities increased in the first 2 wk after treatment, then declined in tumor-bearing livers to levels similar to those in non-tumor-bearing livers. (64 refs)

78-6767 **A Study of Cyclic Nucleotide Metabolism and the Histology of Rat Liver During 3′-Methyl-4-dimethylaminoazobenzene Carcinogenesis. III. Cyclic GMP Metabolism.** (Eng) Boyd, H. (Dept. Pharmacology, Univ. Miami Sch. Medicine, P.O. Box 520875, Miami, FL, 33152); McAfee, D. A.; Laumen, G.; Rubin, J. J. *Tissue Cell* 10(3): 495-504; 1978.

Cyclic guanosine monophosphate (cGMP) metabolism and guanylate cyclase (GC) activity were studied during the development of liver cholangiocarcinomas in Sprague-Dawley rats fed a diet containing 0.06% 3′-methyl-4-dimethylaminoazobenzene. Tumor incidence at 10 wk was 100%. Changes in GC activity were apparent in soluble (SF) and particulate fractions (PF), with and without added Triton X-100 (0.5%). PF activity without Triton increased slightly in the first 3 wk post-treatment, decreased to 50% of control values at 3-5 wk, and then increased to a sharp peak (300% of control values) at 10 wk. SF activity varied in a roughly inverse manner: it showed no appreciable changes for 3 wk, increased to 180% of control values during wk 3-5, then returned to normal before increasing to a sharp peak at wk 10. This peak correlated with the peak tumor incidence. The activity of SF- and Triton-activated PF enzyme increased in tumor-bearing animals, but even more so in tumor tissues. Cyclic GMP levels in uninvolved tissue dropped to 30%-40% of control values during the first 2 wk, but they increased at 4 wk and reached 160% of control values by 10 wk. SF cyclic GMP-phosphodiesterase was consistently elevated (150% of control values) in treated animals after 1 wk, as were PF activities at 1 μM substrate. Higher substrate concentrations, decreased PF enzyme activity. The ratio of cGMP/cAMP decreased in the following order: < in tumors < uninvolved tissue < controls. (33 refs)

78-6768 **Work-related Origin of Cancer in the No Mouth, Throat, and Larynx.** (Ger) Kup, (Sitzungsberichte der Akademie der Wissenschaften DDR, Berlin, E. Germany). *Akademie der Wissenschaf* (2): 20-25; 1978.

The rarity of cancer of the ear, nose, and throat in relat to the total cancer morbidity makes it difficult to single work-related causes. Among a series of 15 patients seen the author, there were 12 cases of laryngeal carcinoma cases of epipharyngeal cancer, and 1 case of nasal carcino Only three of these patients were nonsmokers. The only p sible association with occupation could be made by six lar geal carcinoma patients: four had occupational exposure naphthalene, and two worked in the tire manufacturing dustry. It is suggested that most of these cancers results fr non-work-related causes. (11 refs)

78-6769 **Pathways of DNA Repair Operating in Ye Treated with the Pyrrolo(1,4)benzodiazep Antitumor Antibiotics.** (Eng) Hannan, M. A. (Div. Medici Chemistry and Pharmacognosy, Coll. Pharmacy, Univ. K tucky, Lexington, KY, 40506); Hurley, L. H. *J Antibiot (kyo)* 31(9): 911-913; 1978.

Two principal pathways for the repair of potentially in tivating lesions produced by anthramycin, sibiromycin a tomaymycin in *Saccharomyces cerevisiae* were identifi These pathways utilize the *RAD* 1 gene product concer with the excision of UV-induced dimers and the *RAD* 52 g product concerned with the repair of ionizing radiation- duced DNA strand breaks. (9 refs)

78-6770 **Application of Ames' Test to Dyes.** (Ita) Vi M. (Laboratorio Chimico Farmaceutico E. G nelli S.p.A., Milan, Italy); Nosotti, A. *Boll Chim Fa* 117(7): 402-415; 1978.

Quinoline yellow, tartrazine, patent blue V, food yellow carmoisine, Allura Red AC and Enocyanine were tested mutagenicity in *Salmonella typhimurium* using the Ames say. None of the substances tested induced mutations. (5 re

78-6771 **A Basis for Short-term In Vivo Carcinogene Bioassay (Meeting Abstract).** (Eng) Cueto, (Carcinogenesis Testing Program, NCI, Bethesda, M 20014); Douglas, J. F. *Pharmacologist* 20(3): 175; 1978. (refs)

78-6772 **The Formation of Dihydrodiols by the Chemi or Enzymic Oxidation of Benz(a)anthrace**

7,12-Dimethylbenz(a)anthracene. (Eng) Tierney, B. ster Beatty Res. Inst., Inst. Cancer Res., Royal Cancer ., Fulham Road, London SW3 6JB, England); Hewer, MacNicoll, A. D.; Giovanni Gervasi, P.; Rattle, H.; sh, C.; Grover, P. L.; Sims, P. *Chem Biol Interact* 23(2): 257; 1978.

uick simple method of obtaining small amounts of s-dihydrodiols (trans-DHD) from benz(a)anthracene) and 7,12-dimethylbenz(a)anthracene (DMBA) is de- ed. The characterized trans-DHD of these hydrocarbons e used as reference compounds in the high-pressure liquid matography (HPLC) analysis of DHD mixtures formed ne metabolism of the parent hydrocarbons by rat liver rosomal preparations, and the formation of several previ- y unreported metabolic non-K-region trans-DHD was cted. The non-K-region DHD trans-1,2-dihydro- dihydroxy-BA and trans-3,4-dihydro-3,4-dihydroxy- together with small amounts of the trans-8,9- 10,11-DHD, were formed when BA was oxidized reaction mixture containing ascorbic acid, ferrous ate, and EDTA. When oxidized in a similar system, BA yielded the K-region DHD trans-5,6-dihydro-5,6- ydroxy-DMBA and the non-K-region DHD trans- dihydro -3,4- dihydroxy-DMBA, trans -8,9- dihydro- dihydroxy-DMBA, trans-10,11-dihydro-10,11-dihy- xy-DMBA, and a trace of the 1,2-DHD. The struc- es and stereochemistry of the DHD were estab- ed by comparisons of their UV spectra and HPLC charac- stics with those of authentic compounds or, when no au- ntic compounds were available, by UV, nuclear magnetic nance, and mass spectral analysis. The metabolic DHD e identified by comparisons of their chromatographic and or fluorescence spectral characteristics with compounds nown structures. The principal metabolic DHD formed n BA and DMBA were the trans-5,6- and ns-8,9-DHD. The 1,2- and 10,11-DHD were identified as or products of the metabolism of BA, and tentative iden- ation of the trans-3,4-DHD as a metabolite was made n fluorescence and chromatographic data. The minor abolic DHD formed from DMBA were the ns-3,4-DHD and the trans-10,11-DHD, but the ns-1.2-DHD was not detected. (23 refs)

6773 **Biochemical Studies on Cultured Epithelium-like Cells.** (Eng) Weisburger, E. K. (Carcinogen tabolism and Toxicology Branch, NCI, Bethesda, MD, 014); Idoine, J.; Elliot, J. M. *In: Rat Liver Neoplasia; Work- p on Rat Liver Neoplasia held by William F. Merrell, Co. Woods Hole, October, 1974.* William F. Merrell, Co. oods Hole, MA): 288 pp.; 220-227; 1978.

ntaneous transformation and aryl hydrocarbon hydroxy- e (AHH) activity were monitored in eight epithelial cell es derived from the livers of 7- to 10-day-old Fischer rats. initial assay, the specific AHH activity was 8.3-13.4 its/mg protein/min incubation at 37 C. Of four lines kept in continuous culture, the AHH activity of one was high at the end of 6 mo, the activity of another showed only trace levels, and the activities of the other two remained constant. No tumors developed in animals inoculated with cells from two of the four lines, whereas one animal each developed a tumor (out of each experimental group of 8 rats) following inoculation with cells from the other two lines. AHH activity increased following treatment of cultures with benz(a)anthracene, 7,12-dimethylbenz(a)anthracene, 3-methylcholanthrene, and, to a lesser extent, with phenobarbital. The data indicate that there are biochemical differences in epithelial cell lines derived from the same host tissue and that the level of AHH activity cannot be used as a criterion for the transformed or normal status of cells in culture. (9 refs)

78-6774 **Development and Characterization of Mammary Tumors and Mammary Dysplasias Induced with 7,12-Dimethylbenz(a)anthracene in Lewis Rats.** (Eng) Haslam, S. N. (Univ. California, Berkeley, Berkeley, CA). *Diss Abstr Int B* 39(2): 503; 1978. (no refs)

78-6775 **Induced Cancer of the Mammary Gland in Rats.** (Rus) Kisliakova, N. D. (Hormonal Lab., Res. Inst. Oncology, Rostov-on-Don, USSR); Verevkina, G. A.; Ogorodnikova, L. S.; Kucherova, T. I. *Vopr Onkol* 24(8): 93-97; 1978.

A new method for the mass induction of experimental cancer of the mammary gland in rats is described. To stimulate proliferation in the mammary gland epithelium, random-bred albino rats were fed fresh human placenta (5-6 g/day), which contains large amounts of estrogens and progesterone, for 1.5 mo. One week after the start of this treatment, the animals received dimethylbenz(a)anthracene (DMBA: 10 mg, intragastrically). Ten days later rats received a second dose of DMBA and, 1 mo later, a third dose. Mammary gland tumors were induced in 22/26 rats (1 rat developed a uterine tumor). Tumors were first detected within 1.5 mo of administration of the last DMBA dose. Histologically, the tumors were similar to glandular human breast carcinoma. (7 refs)

78-6776 **Developmental Stage of the Rat Mammary Gland as Determinant of its Susceptibility to 7,12-Dimethylbenz(a)anthracene.** (Eng) Russo, I. H. (Experimental Pathology Lab., Dept. Biology, Michigan Cancer Foundation, 110 E. Warren Ave., Detroit, MI, 48201); Russo, J. *J Natl Cancer Inst* 61(6): 1439-1449; 1978.

Mammary gland development was compared in 80 normal Sprague-Dawley (SP) virgin rats, aged 2-112 days, and 60 SD virgin rats that, at age 55 days, were treated with 7,12-dimethylbenz(a)anthracene (DMBA: 10 mg/100 g intragastrically). Animals of both groups were killed weekly and their

mammary glands were examined in whole-mount preparations. During the first wk of postnatal life, the rat mammary gland was composed of a single lactiferous duct with 3-5 secondary branches termed terminal end-buds (TEB). The TEB grew in size and number for 21 days, then differentiated mainly into alveolar buds (AB). The AB increased steadily until age 70-84 days and differentiated into lobules with the onset of the estrous cycle at 35-42 days. Beginning at age 14 days, undifferentiated TEB's decreased in size and diameter to become terminal ducts (TD), a process that persisted until age 84 days. Therefore, in 84-day-old animals, most TEB's had differentiated into AB or TD. DMBA was administered to the rats at a time when differentiation into AB should have been rapidly progressing and TEB's decreasing. However, the number of TEB's remained constant or decreased only slightly from 5.4 to 4.6 TEB/mm^2. Between days 14 and 21, TEB's began increasing markedly in size (103.0 to 226.3 μ) and were termed intraductal proliferations (IDP). Mitotic activity was high in IDP's, which evolved into microtumors (400 to 750 μ) with the characteristics of adenocarcinoma. In the DMBA-treated animals, decreases in AB and lobules were correlated inversely with the increase in TEB and TD. Although these types of differentiations have not been proven conclusively in humans, there is evidence for an analogous mechanism in the development of human breast carcinoma. (32 refs)

78-6777 **The Effects of UV Light and 7,12-Dimethylbenz(*a*)anthracene (DMBA) on C57BL Mouse Melanocytes (Meeting Abstract).** (Eng) Blog, F. B. (Dept. Dermatology, Erasmus Univ., Rotterdam, Netherlands); Szabo, G. *J Cell Biol* 79(2, part 2): 34a; 1978. (no refs)

78-6778 **Alteration of Pituitary Hormone Secretion in Rats During the Induction of Mammary Tumors by Dimethylbenzanthracene.** (Fre) El Abed, A. (Laboratoire des Hormones polypeptidiques, C.N.R.S., 91190 Gif-sur-Yvette, France); Valens, M.; Langlois, Y.; Kerdelhue, B. *C R Acad Sci [D] (Paris)* 285(16): 1483-1486; 1977.

The secretion of pituitary hormones in various phases of the estrous cycle was studied in female Sprague-Dawley rats during the induction of mammary tumors by 9,10-dimethyl-1,2-benzanthracene (DMBA). Palpable mammary tumors usually appeared in the rats during the 14th cycle after the administration of 15 mg DMBA by gastric tube. Serum concentrations of luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin (PRL), thyroid-stimulating hormone (TSH), and gonadotrophic hormone (GH) were measured on the morning and afternoon of the proestrus and estrus phases of the 2nd-14th cycles after drug administration. An immediate effect of the carcinogen was a decrease in the preovulation peaks of LH and FSH, observed in the afternoon of proestrus; at the same time, concentrations of PRL remained elevated. Concentrations of GH and TSH were usually lower in the DMBA-treated rats. Apparent pituitary hormone secretion is altered in rats susceptible mammary tumor formation by DMBA. (17 refs)

78-6779 **Role of Pineal Gland in Aetiology and Tre ment of Breast Cancer (Letter to Editor).** (Er Tapp, E. (Group Lab., Preston Royal Infirmary, Presto Lancashire, England). *Lancet* 2(8097): 1001-1002; 1978.

Hypersecretion of the pineal gland may be implicated in t etiology of breast cancer. Melatonin increases the secreti of prolactin, a substance implicated in the development breast cancer. Dimethylbenzanthracene-induced mamma tumors in rats show increased malignancy if melatonin prolactin is given. Moreover, suppression of the pineal gla under conditions of continuous daylight reduced the in dence and degree of malignancy of breast tumors. (5 refs

78-6780 **Morphological Changes in the Development 7,12-Dimethylbenz(a)anthracene-induced R Mammary Tumors.** (Jpn) Kobuchi, K. (Dept. Surge Okayama Univ. Medical Sch., Shikata-cho, Okayama 7(Japan). *Okayama Igakkai Zasshi* 90(3/4): 313-334; 1978

7,12-Dimethylbenz(a)anthracene (DMBA: 20 mg) was a ministered by gastric intubation to 55-day-old Sprague-Da ley rats, and morphological changes occurring during mar mary gland carcinogenesis were followed. Rats (2-3) we sacrificed daily during the first week after DMBA admin tration, and then weekly up to 20 wk. At each stage, mar mary glands were examined by the whole-mount metho optical microscopy, and electron microscopy. On day 4 aft DMBA administration, mammary epithelial cells at the pe pheral portion of the duct showed dilatation of the endopla mic reticulum and Golgi apparatus. By 2 wk, hypersecreti was well-established. At 4 wk, the epithelial cells were atr phied and their intracellular organelles were regressed. Ho ever, myoepithelial cells displayed cytoplasmic extensio that surrounded mammary epithelial cells. The stron around the ductules showed marked proliferation. At 7 w hyperplastic alveolar nodules were found. Among some ra stroma growing around the ductules became fibroadenom tous. At 9 wk, tumors (tubular adenocarcinomas) were palp ble. Electron microscopy of the carcinoma demonstrated increased nucleocytoplasmic ratio, nuclear irregularitie hypertrophy of the nuclear membrane, and enlargement the intracellular space. (31 refs)

78-6781 **Measurement of Aryl Hydrocarbon Hydroxy lase and NADH-dependent Cytochrome *c* R ductase Activities in Mitogen-activated Human Ly phocytes.** (Eng) Kouri, R. E. (Dept. Biochemical Oncolog Microbiological Associates, Bethesda, MD, 20014); Imblun

L.; Prough, R. A. *In: Prevention and Detection of Cancer. ceedings of the Third International Symposium on Detec- and Prevention of Cancer Held by the International Study oup for the Detection and Prevention of Cancer in New rk, April 26 - May 1, 1976.* International Study Group for Detection and Prevention of Cancer. (New York, NY): . 2(part 1), 2404 pp.; 1659-1676; 1978.

ctors that influence mitogen activation and induction of l hydrocarbon hydroxylase (AHH) activity in cultured man lymphocytes were examined. The most effective mito- s for lymphocyte activation were phytohemagglutinin HA), PHA plus pokeweed mitogen, leucoagglutinin. The IH activity of cultured human lymphocytes was influenced factors such as type and lot of fetal calf serum, type and of mitogen, kind of inducer, initial cell concentration, and gree of mitogen activation. The degree of 3-methyl- olanthrene (3-MC)-induced (and noninduced) AHH ac- ity paralleled the degree of mitogen activation. At concen- tion of 2-5 μM, benz(a)anthracene and 5,6-benzoflavone iciently induced AHH activity to levels similar to that in- ced by 3-MC. Presentation of AHH activity based on level cytochrome *c* reductase activity rather than on the number cells or total DNA resulted in consistently lower interassay riation. Two other factors that helped yield a lower in- assay variation were the use of lot No. 88973 fetal calf um, which resulted in basal AHH levels 5-15 times above ro time fluorescence values, and the use of an initial cell ncentration of 1.5 x 10^6 cells/ml, which routinely resulted peak AHH activity for both 3-MC-induced and control ltures at 72 hr. (42 refs)

-6782 **Induction of Tumor-Cytostatic Macrophages by Phorbol-12.13-Diester (Meeting Abstract).** ng) Grimm, W. (Institut f. Immunologie der Universitat, eidelberg, W. Germany); Gemsa, D. *Z Immunitaetsforsch* 5(1): 19; 1978. (no refs)

-6783 **Electrochemical Investigations on Several Dimethylbenzo(a)pyrenes.** (Eng) Park, S. M. ept. Chemistry, Univ. New Mexico, Albuquerque, NM, 131); Michnovicz, J. J.; Daub, G. H. *Anal Biochem* 90(1): 4-388; 1978.

ectrochemical studies were made of five dimethylbenzo(a)- rene (DMBP) derivatives, 1,3-, 1,6-, 2,3-, 3,6-, and 5-DMBP, all of which have stronger carcinogenicity than nzo(a)pyrene (BP). A three-electrode cell housing a plati- m disk working electrode, a Pt wire auxiliary electrode, and a silver wire pseudoreference electrode were used to record the cyclic voltammetry and chronopotentiometry in (1:1) acetonitrile-benzene solns with tetra-n-butylammonium perchlorate as a supporting electrolyte. The oxidation and reduction of DMBP's were demonstrated to be reversible one-electron processes, forming the cation and anion radicals, respectively, as the electrode reaction products. Cyclic voltammograms indicated that the cation radicals are very stable. The half-lives calculated from pseudo-first-order decay rate constants were estimated to be 150, 11.4, and 7.7 sec for the 1,3-, 2,3-, and 3,6-DMBP's, respectively. The one-electron electrooxidations may be due to the stabilization of the cation radicals by methyl substituents and to the dryness of the solvent. The cation radicals of the DMBP's were more stable than those of benzo(a)pyrene (previous study). Studies of reactions of cation radicals with nucleophiles such as water and pyridine showed that blocking at the 6-position lowered the reactivity of the cation radical toward water, a mild nucleophile. Pyridine was too strong to be affected by 6-position blocking. (27 refs)

78-6784 **Benzo(a)Pyrene 7,8-Dihydrodiol-9,10-oxide Modification of DNA: Relation to Chromatin Structure and Reconstitution.** (Eng) Yamasaki, H. (Dept. Medicine, Columbia Univ. Coll. Physicians and Surgeons, 701 W. 168th St., New York, NY, 10032); Roush, T. W.; Weinstein, I. B. *Chem Biol Interact* 23(2): 201-213; 1978.

DNA was modified by in vitro reaction with the 7,8-dihydrodiol-9,10-oxide of benzo(a)pyrene (BPDE), and the effects of this modification on the in vitro reconstitution of nucleosome structures were examined. In addition, intact chromatin (CT) was reacted with BPDE, and the distribution of the covalently bound BP residues was studied. Purified duck reticulocyte DNA modified by incubation with BPDE was more susceptible to partial digestion by the single-strand-specific endonuclease S_1 than unmodified DNA, suggesting slight denaturation of the helix at sites of modification. CT that was reconstituted using this carcinogen-modified DNA and unmodified CT-associated proteins showed the same kinetics and extent of digestion by *Staphylococcal* nuclease and similar nucleosome profiles on sucrose density gradient centrifugation as those obtained with native CT or CT reconstituted with unmodified DNA. Polyacrylamide gel electrophoresis of DNA fragments obtained from nuclease digests of the reconstituted CT's suggested that the CT containing carcinogen-modified DNA had the same subnucleosome structure as that reconstituted with unmodified DNA. After intact duck reticulocyte CT was reacted directly with BPDE, nuclease digestion studies indicated that 65% of the carcinogen was bound to the 'open' regions of CT and 35% to 'closed' regions (ie, regions highly susceptible to digestion by *Staphylococcal* nuclease vs regions relatively resistant to digestion). The results indicate that although covalent binding of a BP derivative to DNA produces local

distortions in conformation of the helix, this modification does not appear to interfere with the ability of the DNA to associate with histones to form nucleosome structures. Although DNA in the open regions of CT is more susceptible to reaction with the BP derivative, there is appreciable reaction with the DNA associated with histones. (46 refs)

78-6785 **Uptake, Binding to Cytoplasmic Protein, Translocation to the Nucleus and Morphological Transformation of Human Cells by Benzo(a)pyrene and 7,12-Dimethylbenzanthracene.** (Eng) Ekelman, K. B. (Ohio State Univ., Columbus, OH, 43210). *Diss Abstr Int B* 39(2): 499-500; 1978. (no refs)

78-6786 **Pathologic Changes Induced in Respiratory Tract Mucosa by Polycyclic Hydrocarbons of Differing Carcinogenic Activity.** (Eng) Topping, D. C. (Natl. Inst. Environmental Health Sciences, Research Triangle Park, Durham, NC, 27709); Pal, B. C.; Martin, D. H.; Nelson, F. R.; Nettesheim, P. *Am J Pathol* 93(2): 311-324; 1978.

The toxic effects of benzo(e)pyrene (BeP), pyrene, anthracene, benz(a)anthracene (BA), dibenz(a,c)anthracene (DBA), benzo(a)pyrene (BP), and dimethylbenz(a)anthracene (DMBA) were investigated in the respiratory mucosa of male Fischer F-344 rats. These compounds were chosen because they comprise a spectrum of polycyclic hydrocarbons (PCH) ranging from noncarcinogens to initiators, weak carcinogens, and strong carcinogens. Heterotopic tracheal grafts were maintained under the dorsal skin of syngeneic recipients. The grafts were exposed to the test substance from an intraluminal beeswax pellet, which released the material slowly over 8 wk. The histopathologic effects were periodically assessed semiquantitatively. All PCH exhibited varying degrees of toxicity for the respiratory epithelium and submucosa. BeP showed the least toxicity, followed by pyrene and anthracene. BA and DBA caused marked epithelial and submucosal changes: epithelial hyperplasia, undifferentiated epithelium, and squamous metaplasia and marked mononuclear infiltration in the subepithelial connective tissue. With BP, the epithelial and submucosal changes were similar but stronger. DMBA was the most toxic substance, causing epithelial necrosis followed by generalized keratinizing squamous metaplasia; the subepithelial changes consisted of an early acellular exudate and, at 8 wk, marked condensation and hyalinization of the lamina propria. The toxic response pattern of the tracheal mucosa to carcinogens was characterized by the chronicity of epithelial and connective tissue damage, as opposed to the short-lived hyperplastic and inflammatory response elicited by the noncarcinogens and v initiators. (21 refs)

78-6787 **Histochemical Patterns of a Few Key Carb drate Metabolic Enzymes During Hepato cinogenesis (Meeting Abstract).** (Ger) Hacker, H. J. (He berg, W. Germany); Bannasch, P. *Zentralbl Allg Pa* 122(3): 289; 1978. (no refs)

78-6788 **Inducibility of Aryl Hydrocarbon Hydroxy in Cultured Human Lymphocytes.** (Eng) Fle er, K. A. (Dept. Tropical Medicine, Univ. Liverpool, Box 147, Liverpool L69 3BX, England); Price Evans, D Canning, M. V. *J Med Genet* 15(3): 182-188; 1978.

The method for estimating aryl hydrocarbon hydroxy (AHH) activity in cultured human lymphocytes was m fied in an attempt to obtain reproducible values for A induction. However, none of the modifications produced level of reproducibility required for quantitative genetics poses. (18 refs)

78-6789 **Vaginal and Cervical Squamous Cell Dysp in Women Exposed to Diethylstilbestrol Utero.** (Eng) Burke, L. (Beth Israel Hosp., 330 Brook Ave., Boston, MA, 02215); Antonioli, D.; Rosen, S. *A Obstet Gynecol* 132(5): 537-544; 1978.

Pelvic, colposcopic, and histologic examinations were formed on 250 patients with a known or suspected his of in utero exposure to diethylstilbestrol (DES). (Expo was confirmed in 205 cases.) Colposcopically abnormal a were graded for severity according to predetermined crit and biopsy evaluation was made for adenosis in vaginal sp mens and squamous metaplasia, glandular or squamous plasia, nonglycogenated mucosa, and dysplasia in both v nal and cervical specimens. No glandular or squamous carcinomas were noted, but a nonneoplastic abnormality found in biopsy specimens of 82% of the women. Gross normalities included cervical columnar epithelium in women and a cervicovaginal hood in 147. Adenosis was sent in vaginal walls, fornices, and/or hood in 185 cases. poscopically abnormal areas were present in vaginas and hoods of 211 patients. Fifteen patients had squamous dysplasia, the degree of which was mild in 11 and mode in 4 cases. The dysplasia involved the cervix in 14 pati and the vagina in 4. Patients with cervical mosaic and w epithelium had dysplasia on biopsy much more freque than patients with similar colposcopic appearances in vagina. Thus, colposcopic data on cervical dysplasia can

applied to the evaluation of dysplasia in vaginal adenosis hout modification. (16 refs)

-6790 **Comparative Sensitivity of Animals of Various Species to the Carcinogenic Effect of Tryptoan Metabolites.** (Rus) Khrustalev, S. A. (Lab. Systemic ood Diseases, Cancer Res. Center, Moscow, USSR). *Patol iol Eksp Ter* (4): 61-63; 1978.

e carcinogenic activity of tryptophan metabolites in guinea gs, Syrian hamsters, and random-bred rats was compared. imals of each species were divided into two groups: Group vas inoculated sc with 2-aminoacetophenone (2-AAP) and roup 2 was inoculated sc with 3-indolylacrylic acid (3-IAA) 2- to 3-day intervals. Both groups received inoculations for 5 mo; the total dose of each agent was 500-740 mg for inea pigs, 200 mg for hamsters, and 200 mg for rats. The ukemogenic activity of 2-AAP and 3-IAA was most prounced in the hamsters (there were 6 cases of lymphosarma, 2 cases of myeloid leukemia, 2 cases of lymphoid leumia, and 1 case of plasmacytic leukemia of hemopoietic lls). Among the rats there were seven cases of lymphosarma, and among the guinea pigs there was one case of lymoid leukemia. Both metabolites also induced various begn and malignant tumors in the hamsters (6 insulinomas the pancreas, 1 adenoma of the pancreas, 2 liver cholangimas, 1 papilloma of the vagina, 3 fibrosarcomas and fiomas, 1 melanoma, and 1 papillary carcinoma of the uriary bladder). Both metabolites also induced various tumors rats (2 fibromas, 1 fibrosarcoma, 1 cystic epithelioma, 1 varian folliculoma, 1 uterine myxofibroma, 6 mammary and carcinomas). (7 refs)

8-6791 **Role of Hormones in Mammary Neoplasia.** (Eng) Nandi, S. (Dept. Zoology, Univ. Calirnia, Berkeley, CA, 94720). *Cancer Res* 38(11, part 2): 046-4049; 1978.

A hypothesis for the role of hormones in mammary neoplasia s well as neoplasia in other endocrine organs and target tisues is presented. It is assumed that hormones are not carinogenic by themselves but that they modify the host and/or arget tissues during the events initiated by carcinogens such s viruses, chemicals, or radiation. The hypothesis is based n the observations that hormones are involved in regulating ell division in normal mammary cells, the emergence of ovrt mammary tumors requires hormonal stimulation of cells eceiving a carcinogenic stimulus, normal cells have finite livisonal life but neoplastic cells are immortal, and normal nammary cells might inhibit the growth of small numbers of preneoplastic and neoplastic cells. The hypothesis is that normones have at least two functions in mammary carcinogenesis initiated by direct-acting carcinogens. First, hormones are necessary for DNA synthesis and mitosis of the nitial transformed cells and, consequently, for their conversion into fixed transformed cells with heritable characteristics. Second, hormones stimulate the rapid growth of normal cells with finite divisional life, leading to a reduction in their number in localized areas surrounding the transformed cells or in the tissue as a whole. This releases the transformed cells from the growth inhibitory influence of normal cells, allowing the emergence of overt tumors. (48 refs)

78-6792 **Two In Vivo Assays for Mutagenicity Compared: The Sperm Abnormality and Micronucleus Assays (Meeting Abstract).** (Eng) Bruce, W. R. (Dept. Medical Biophysics, Univ. Toronto, Toronto, Canada); Heddle, J. A. *Mutat Res* 53(2): 159-160; 1978. (no refs)

78-6793 **The Formation of a Large Molecular Weight Form of ACTH by Chemically-induced Rat and Mouse Lung Tumors (Meeting Abstract).** (Eng) Khan, M. N. (Molecular Pharmacology, Biochemistry Section, Lab. Pharmacology, NIEHS, Research Triangle Park, NC, 27709); Ghosh, A.; Linnoila, I.; Nettesheim, P.; DiAugustine, R. P. *Environ Health Perspect* 20: 232-233; 1977. (1 ref)

78-6794 **Dose-Effect Studies on Estrogen Induced Mammary Cancers in Mice.** (Eng) Rudali, G. (Equipe de Recherche 190 du C.N.R.S., Fondation Curie, 26, Rue d'Ulm, 75231 Paris, Cedex 05, France); Jullien, P.; Vives, C.; Apiou, F. *Biomedicine* 29(2): 45-46; 1978.

Castrated male (C3H x RIII)F1 mice were treated with graded doses of estradiol-17β and estrone in a life-span experiment to determine to what extent the carcinogenic activity of estrogens in the mammary gland was dose-related. The mice were castrated at age 25 days; on the same day, paraffin pellets containing estradiol-17β were implanted sc for continuous resorption. These pellets contained 1, 2.5, 5, 10, or 100 μg of hormone. Other castrated mice received estrone po in the food at concentrations of 0.02, 0.2, or 2 ppm, corresponding to daily intakes of 0.06, 0.6 and 6 μg, respectively. In addition, castrated females were ovariectomized and treated with the lower doses of the estrogens to see if they were sufficient to induce a vaginal estrus. Although the lower doses of both hormones induced vaginal estrus, they did not produce mammary tumors in the males. With the higher doses, however, the mammary tumor incidence was 95.8%-100%. These findings can be compared with clinical evidence in humans that continuous ingestion of low doses

of estrogens does not enhance breast cancer development. (44 refs)

78-6795 **Liver Tumours Associated with Oral Contraceptive Agents (Meeting Abstract).** (Eng) Britton, W. J. (A. W. Morrow Dept. Gastroenterology, Royal Prince Alfred Hosp., Sydney, Australia); Gallagher, N. D.; Little, J. M. *Aust NZ J Med* 8(5): 559; 1978. (no refs)

78-6796 **Tumor Promoter Inhibits Production of Liver Retinol Binding Protein (Meeting Abstract).** (Eng) Borek, C. (Coll. Physicians Surgeons, Columbia Univ., New York, NY); Smith, J. E. *J Cell Biol* 79(2, Part 2): 78a; 1978. (no refs)

78-6797 **Factors Affecting the Induction of Chromosomal Aberrations by Cadmium in Chinese Hamster Cells (Meeting Abstract).** (Eng) Deaven, L. L. (Cellular and Molecular Biology Group, Los Alamos Scientific Lab., Univ. California, Los Alamos, NM, 87545); Campbell, E. W. *J Cell Biol* 79(2, part 2): 131a; 1978. (no refs)

78-6798 **Hormonal Control of Preneoplastic Epidermal Cells During Carcinogenesis in Mice (Meeting Abstract).** (Eng) Lupulescu, A. (Dept. Dermatology, Wayne State Univ., Detroit, MI); Rogers, J.; Birmingham, D. *J Cell Biol* 79(2, part 2): 187a; 1978. (no refs)

78-6799 **The Influence of Nutrition on the Growth of Experimental Kidney Tumors in Rats (Meeting Abstract).** (Eng) Hartig, F. (Mannheim, W. Germany); Hebold, G. *Vet Pathol* 15(4): 574; 1978. (no refs)

78-6800 **Mesotheliomas Induced by Sterigmatocystin in Wistar Rats.** (Eng) Terao, K. (Res. Inst. Chemobiodynamics, Chiba Univ., Inohana 1-8-1, Chiba 280, Japan). *Gann* 69(2): 237-247; 1978.

The direct carcinogenic potency of sterigmatocystin (SMC) to the peritoneum after repeated ip injections was investig ed in male Wistar rats. Three groups of rats received ip inj tions of SMC, O-acetylsterigmatocystin (AcO-SMC), dihydrosterigmatocystin (dihydro-SMC) 1 x/wk for 23 and they were observed for 80 wk. Only SMC produc mesothelioma in 20/40 rats given a total dose of 20-25 n No mesotheliomas were found in rats injected w AcO-SMC or dihydro-SMC. Both epithelioid and mesench mal mesotheliomas were induced by SMC. Hepatocellu carcinomas were found in one rat treated with SMC and five given AcO-SMC. These results suggest that SMC is potent carcinogen when administered ip. Although bo dihydro-SMC and SMC formed fine, needlelike crystals wh injected ip, dihydro-SMC did not produce any mesothe omas. Dihydro-SMC has no double bond in the terminal ran ring; this double bond has been postulated as an impo tant determinant of the acute toxicity and carcinogenicity aflatoxin B_1 in rats. It is suggested, therefore, that the ca cinogenicity of SMC to the peritoneum may be related mo closely to the presence of this double bond than to its physic form in the peritoneal cavity. (28 refs)

78-6801 **Induction by Degraded Carrageenan of Colore tal Tumors in Rats.** (Eng) Wakabayashi, (Res. Inst., Nippon Chemiphar Co., Ltd., Misato-shi, Sait ma, Japan); Inagaki, T.; Fujimoto, Y.; Fukuda, Y. *Canc Lett* 4(3): 171-176; 1978.

The carcinogenicity of degraded carrageenan derived fro the red seaweed *Eucheuma spinosum* was examined in Spr gue-Dawley rats. In the first experiment, rats were divide into four groups of 30 males and 30 females each: Grou 1, 2, and 3 received 10%, 5%, and 1% carrageenan in th diet, respectively, for up to 24 mo, and Group 4 served a control. The rats were sacrificed at various intervals up 24 mo after the start of the experiment. A total of 59/6 Group 1 and 12/60 Group 2 rats developed colorectal squa mous metaplasia; 19/60 and 53/60 rats, respectively, dev loped colorectal tumors. The tumors were squamous cell ca cinomas, adenocarcinomas and adenomas; two Group 1 ra and one Group 2 rat had metastases of squamous cell ca cinomas to the retroperitoneal lymph nodes. In a second ex periment, 20 animals of each sex were given a 5% aqueou soln of degraded carrageenan in the drinking water for 15 m Metaplasia was noted in all 40 rats, and 11 developed tumor In addition to the tumor types found in the first experimen one myosarcoma was also observed. In the third experimen rats were divided into three groups of 15 males and 15 female each. Group 1 was given 5 g/kg and Group 2 1 g/kg degraded carrageenan by stomach tube for 15 mo. Metaplasi was noted in all Group 1 rats and in 11/30 Group 2 rats Adenocarcinomas and adenomas were noted in eight Grou 1 animals. No colorectal metaplasia or tumors were noted i control rats in all three experiments. These findings indicat that degraded carrageenan is carcinogenic to the colorecta epithelium of the rat. (9 refs)

6802 The Use of Short-Term Tests to Measure the Preventive Action of Reducing Agents on For-ion and Activation of Carcinogenic Nitroso Compounds.
g) Lo, L. W. (Cancer Res. Centre, Univ. British Co-bia, Vancouver V6T IW5, Canada); Stich, H. F. *Mutat* 57(1): 57-67; 1978.

effect of reducing agents on the nitrosation of methyl-nidine (MG) and on the in vitro activation of dimethylni-amine (DMN) was examined in cultured human fibrob-s. The reducing agents were sodium ascorbate, cysteine, eamine, and propyl gallate. The addition of sodium ascor-e to an $NaNO_2$ and MG mixture resulted in reduced DNA air synthesis. The inhibitory action of sodium ascorbate nitrosation of MG was also observed when the extent of omosome aberrations was measured and when the ne-forming capacity of human fibroblasts was estimated. A repair synthesis of cultured human fibroblasts incubat-with a rat liver microsomal activation system and DMN greatly reduced in the presence of the reducing agents. e inhibitory effect could have been exerted during activa-n of DMN, or it could also be due to the trapping of free icals formed during activation. The results do not distin-sh between these two possibilities. Alkaline sucrose gradi-analysis showed that sodium ascorbate inhibited the shift smaller DNA fragments that was observed when cultured s were exposed to liver microsome-activated DMN. These ults indicate that DNA repair synthesis is a suitable rt-term test for studying the numerous interactions be-en several carcinogenic agents and for estimating the acity of inhibitory agents to affect formation and activa-n of chemical carcinogens. (45 refs)

See also:

*(Rev.): 78-6601, 78-6603, 78-6604, 78-6605, 78-6606, 78-6607, 78-6608, 78-6609, 78-6611, 78-6612, 78-6613, 78-6614, 78-6615, 78-6616, 78-6617, 78-6618, 78-6619, 78-6621, 78-6622, 78-6623, 78-6624, 78-6625, 78-6626, 78-6627, 78-6628, 78-6629, 78-6630, 78-6631, 78-6634, 78-6635, 78-6636, 78-6637, 78-6638, 78-6639, 78-6640, 78-6641, 78-6642, 78-6643, 78-6644, 78-6645, 78-6646, 78-6647, 78-6648, 78-6649, 78-6650, 78-6651, 78-6652, 78-6653, 78-6654, 78-6655, 78-6656, 78-6657, 78-6658, 78-6659, 78-6660, 78-6662, 78-6663, 78-6664, 78-6697, 78-6701, 78-6702, 78-6703, 78-6706, 78-6707.

*(Phys.): 78-6805, 78-6808, 78-6810, 78-6815, 78-6817, 78-6836.

*(Viral): 78-6862, 78-6868, 78-6899, 78-6908, 78-6933, 78-6969, 78-6970.

*(Immun.): 78-6984, 78-6994, 78-6998, 78-7011, 78-7033, 78-7041, 78-7042, 78-7043, 78-7045, 78-7046, 78-7048, 78-7049, 78-7051, 78-7053, 78-7059, 78-7061, 78-7063, 78-7064.

*(Path.): 78-7075, 78-7076, 78-7088, 78-7095, 78-7107, 78-7110, 78-7113, 78-7114, 78-7122, 78-7125, 78-7126, 78-7133, 78-7141.

*(Epid.-Biom.): 78-7149, 78-7150, 78-7151, 78-7156, 78-7162, 78-7163, 78-7172, 78-7173, 78-7174, 78-7176, 78-7181, 78-7183, 78-7184.

78-6803 **Malignant Melanoma of Skin and Sunspot Activity (Letter to Editor).** (Eng) Wigle, D. T. (Bureau Epidemiology, Lab. Centre Disease Control, Health and Welfare Canada, Ottawa, Canada K1A 0L2). *Lancet* 2(8079): 38; 1978.

Studies in the US and Canada showed that the incidence of malignant melanoma during 1935-75 varied cyclically, with the peaks correlating closely with periods of peak sunspot activity. The increased flux of cosmic rays during peak sunspot activity may destroy stratospheric ozone, so that more UV radiation reaches the earth's surface. (no refs)

78-6804 **Re: "Mathematical Models of Age and Ultraviolet Effects on the Incidence of Skin Cancer among Whites in the United States" (2 Letters to Editor).** (Eng) Lee, J. A. (Dept. Epidemiology, Sch. Public Health, Univ. Washington, Seattle, WA, 98195); Fears, T. R.; Scotto, J.; Schneiderman, M. A. *Am J Epidemiol* 107(3): 259-262; 1978.

Discrepancies between the regression coefficients for the incidence of nonmelanoma skin cancer and malignant melanoma with increasing age have implied that both these conditions are related to annual dose rather than cumulative lifetime UV exposure. It is suggested, however, that the similarity of the regression coefficient relating latitude and the coefficient relating age to the incidence of nonmelanoma skin cancer indicates that these tumors are produced by the cumulative effect of UV damage; this cumulative relationship may also hold for melanoma. In a rebuttal, it is held that since a flat age/nonmelanoma incidence is not found, neither melanoma nor nonmelanoma incidences are directly related to total UV exposure. It is suggested that nonmelanoma incidence is related to the cumulative UV dose and that melanoma incidence is related to the annual UV dose. (14 refs)

78-6805 **Interaction of Near-Ultraviolet Radiation and Irradiated L-Tryptophan in the Production of Mutations in *Escherichia coli*.** (Eng) Webb, R. B. (Div. Biological and Medical Res., Argonne Natl. Lab., Argonne, IL, 60439); Yoakum, G. H.; Perou, J.; Eisenstark, A. *Mutat Res* 51(3): 427-432; 1978.

The interaction between near-UV radiation and preirradiated tryptophan (TP) in *Escherichia coli* growing in chemostat cultures was studied. Near-UV radiation alone produced T5-resistant mutants in *E. coli* WP2 culture at a rate of 25.3 x 10^{-8} mutant/cell/day/watt m^{-2}. It produced 59.5 x 10^{-8} mutant/cell/day/watt m^{-2} in the excision-deficient strain WP2 When TP was present in the culture during near-UV tre ment, the rate of mutagenesis was increased two-fold f strain WP2 and seven-fold for strain WP2s. In the absen of near-UV radiation, TP increased the mutation rate by factor of 1.3 in strain WP2 and by a factor of 1.7 in stra WP2s. The presence of unirradiated TP (5-10 mg/liter) r duced the rate of near-UV mutagenesis. The data suggest th the nonmutagenic repair of lesions produced by the intera tion of components of TP and near-UV radiation requires t *uvrA*+ endonuclease. (20 refs.)

78-6806 **Effects of Dietary Constituents on Ultraviol Light-mediated Carcinogenesis.** (Eng) Black, S. (Photobiology Lab., Veterans Admin. Hosp., Housto TX, 77030); Chan, J. T.; Brown, G. E. *Cancer Res* 38(5 1384-1387; 1978.

The effects of dietary supplements of antioxidants and e zyme inducers on UV-mediated carcinogenesis in fema hairless mice were investigated. The animals received eith a (1) regular, balanced, laboratory meal, (2) regular meal su plemented with 0.05% (wt/wt) phenobarbital, (3) regul meal with disulfiram (2 mg/g meal), (4) regular meal wi 0.5% (wt/wt) butylated hydroxytoluene (BHT), or (5) reg lar meal with 0.1% (wt/wt) reduced glutathione. At the en of 17 wk, the animals in Group 3 were transferred to a regul meal because of wt loss. After 10 days, the mice received U radiation treatments 5 days/wk through week 17. The initi suberythemic dose was 0.84 joule/cm^2/day; it was increase every 2 wk by 0.34 joule/cm^2 until a daily dose of 2.1 joules/cm^2 was given.An accumulative dose of 152 joules/cm was administered. The reduced glutathione diet had no e fect on tumor incidence, but the BHT, phenobarbital, an disulfiram diets all significantly suppressed the initiation an development of actinic lesions and tumors. Analysis of th percentage of animals bearing lesions and tumors, percentag of animals bearing tumors, and numbers of tumors/anima indicated that disulfiram provided the greatest protectio Tumor inhibition thus appears to be due to the induction o systemic physiological responses. (39 refs)

78-6807 **Inhibition of UV-induced DNA Repair at Di ferent Steps by Quinacrine and Anthralin.** (Eng Kulkarni, M. S. (Lab. Molecular Biology, Univ. Alabama Birmingham, AL, 35294); Yielding, K. L. *Biochem Biophy Res Commun* 83(4): 1531-1537; 1978.

The effects of anthralin (AT) and quinacrine (QA) on DNA

r synthesis were evaluated in L1210 cells, a mouse lymlastoma line. The cells were labeled with ^{3}H-thymidine, iated with UV light, and incubated for 15 or 45 min with ithout QA or AT (both, 50 μM). The appearance and pearance of single-strand breaks was followed by nud sedimentation in neutral sucrose gradients. QA ed the reduction in nucleoid sedimentation rate resultom UV irradiation. After 15 min of post-UV incubation QA, these nucleoids still sedimented like those from adiated cells. With 45 min post-UV incubation, howevie sedimentation profile resembled that of irradiated cells 15 min of post-UV incubation without QA. These findsuggest that QA inhibits the UV endonuclease step in r. AT apparently increased the extent of single-strand nentation seen at 15 min post-UV incubation. There was nce for repair after 45 min post-UV incubation with AT, dicated by an increased nucleoid sedimentation rate. , AT enhanced the initial appearance of nicked DNA wed by a return to normal, but QA delayed the nicking ess. Although both agents inhibit repair synthesis, they produce different biological effects. (25 refs)

5808 **Mutagenicity and Carcinogenicity of 8-MOP/UVA in Cell Cultures.** (Eng) Burger, P. M. ot. Dermatology, Univ. Medical Centre, State Univ. en, Leiden, Netherlands); Simons, J. W. *Bull Cancer (Pa-* 65(3): 281-282; 1978.

ants deficient for the enzyme oxanthine-guanine-phosphoribosyltransferase (HGPRT) selected in V-79 Chinese hamster cells and in human oid skin fibroblasts (HSF) after application of the photonotherapeutic (PUVA-therapy) regimen of 8-methoxyalen (8-MOP) (10 μg/ml) and UV irradiation (0-600 es (J)/m^2). In the V-79 cells, there was a linear relation- between UV dose and mutation frequency. However, respect to varying doses of 8-MOP, a constant number nduced mutants (5.5 x 10^{-8} per μg 8-MOP/ml per J/m^2 he unit dose) was detected. HSF also yielded a constant nber of induced mutants/unit dose of 8-MOP (3.3 x 10^{-8} it dose for dividing cells and 0.6 x 10^{-8}/unit dose for dividing cells). If these results are extrapolated to human helial cells, it is predicted that 7.4 x 10^{-5} mutants/unit e for dividing cells and 1.4 x 10^{-5} mutants/unit dose for -dividing, (or a total of 1.7 x 10^{-5} mutants induced per ion of PUVA therapy) may be expected to arise. A carogenic effect (the induction of cell transformation in C3H 3T3 mouse cells) was also observed. (12 refs)

6809 **8-Methoxypsoralen as a Frameshift Mutagen in Bacteria and Chinese Hamster Cells in the rk--Implications for Genetic Risk in Man (Meeting Abact).** (Eng) Bridges, B. A. (MRC Cell Mutation Unit, iv. Sussex, Falmer, Brighton, England); Mottershead, R. Arlett, C. F. *Mutat Res* 53(2): 156; 1978. (no refs)

78-6810 **Characterization of Sister Chromatid Exchange Induction by 8-Methoxypsoralen plus Near UV Light.** (Eng) Latt, S. A. (Genetics Div., Childrens Hosp. Medical Center, 300 Longwood Ave., Boston, MA, 02115); Loveday, K. S. *Cytogenet Cell Genet* 21(4): 184-200; 1978.

Factors influencing the induction of sister chromatid exchanges (SCE's) in Chinese hamster ovary (CHO) cells by 8-methoxypsoralen (8-MOP) + near-UV light were investigated. Exposure of CHO monolayers to approx 6 x 10^{-6} M 8-MOP or UV light (up to 2 x 10^4 ergs/mm^2, primarily at 365 nanometers) prior to bromodeoxyuridine (BUdR) treatment had little effect on SCE frequency. However, irradiation of cells shortly after 8-MOP addition resulted in a marked increase in SCE's that was dependent on 8-MOP dose and UV dose, but not on the interval between the two. SCE induction by 8-MOP + UV light was compatible with cell survival over multiple cycles. Study of cells that had undergone three cycles of BUdR incorporation indicated that 8-MOP + UV light increased SCE formation during the third cycle. Thus, cells surviving treatment included those damaged and responding with an increase in SCE's. Both the frequency and location of SCE's induced at different times within the DNA synthesis period varied in a manner that indicated that exchange induction was restricted to regions that replicated during or after DNA damage. (56 refs)

78-6811 **Inflammatory Reactions Induced by Ultraviolet Irradiation.** (Eng) Greaves, M. W. (Inst. Dermatology and St. John's Hosp. Diseases of the Skin, Homerton Grove, London E9 6BX, England); Hensby, C. N.; Black, A. K.; Plummer, N. A.; Finchman, N.; Warin, A. P.; Camp, R. *Bull Cancer (Paris)* 65(3): 299-303; 1978.

Human skin irradiated with different wavelengths of the UV spectrum in the presence and absence of anti-inflammatory drugs was examined pharmacologically. In all experiments, human abdominal skin was irradiated; it was examined visually for erythema, and exudate from irradiated cells was collected at different times after irradiation and analyzed by bioassay using the cascade superfusion technique, by radioimmunoassay, and by gas-liquid chromatography-mass spectrometry. Unirradiated skin from the same subject was used as the control. Blood flow (BF) changes were also measured by photoelectric plethysmography. After irradiation with six times the minimal erythema dose (MED) of UVC [$<$290 nanometers (nm) in wavelength], the levels of arachidonic acid (ARA) and prostaglandins (PG)E_2 and F_2 were all increased (1.5-3.0 times control), reaching a max at 18-24 hr, but returned to control levels by 48 hr, by which time the erythema had also subsided. When the PG inhibitor indomethacin (IM) was administered in divided doses beginning 48 hr before irradiation, the levels of PGE_2 and PGF_2 were both held to the control level, but ARA levels were enhanced in both irradiated and nonirradiated skin. IM caused a reduction in BF that correlated with a reduction in visual erythema. Irradiation with 3 MED of UVB (290-320 nm) also

produced peaks in levels of ARA, PGE_2, PGF_2 and other ARA metabolites at 24 hr (5 to 20 times control), which returned to control values by 48 hr. Erythema did not decrease at 48 hr, however, and IM treatment produced only a small change in BF in irradiated skin while apparently completely suppressing PG activity. UVA (320-400 nm) treatment of patients after administration of 8-methoxypsoralen produced no changes in PGE_2 or PGF_2 levels in irradiated areas, but ARA levels were again increased at 24 hr. It is suggested that increased levels of PGE_2 protect epidermal cells from mutagenic action of UVB by increasing cellular levels of cyclic AMP and thus reducing the vulnerable pool of actively dividing cells. (16 refs)

78-6812 **Detection of DNA Repair in Nuclei Isolated from Human Cultured Cells (Meeting Abstract).** (Eng) Robison, S. H. (Dept. Pathology, Thomas Jefferson Univ., Philadelphia, PA); Fansler, B. S. *J Cell Biol* 79(2, part 2): 137a; 1978. (no refs)

78-6813 **Quantitative Changes in Respiratory Enzyme Activity in Premalignant Lesions and Experimentally Irradiated Skin.** (Eng) Pearse, A. D. (Dept. Medicine, Welsh Natl. Sch. Medicine, Heath Park, Cardiff, Wales); Marks, R. *Bull Cancer (Paris)* 65(3): 351-356;1978.

The morphological and cell kinetic findings were compared with metabolic changes within the epidermis of patients exposed to solar radiation to investigate the earliest changes in UV-induced neoplasia. Quantitative enzyme histochemical techniques were employed to examine lesional and paralesional skin from four patients with solar keratoses and one with Bowen's disease. Buttock skin was also sampled from these patients to compare the lesional sun-exposed skin with non-sun-exposed skin. Succinic dehydrogenase (SDH) activity was evenly distributed in buttock skin, and there was very little change in total sun-exposed epidermal SDH activity, but it was significantly reduced in the granular cell layer in lesional and paralesional skin of all patients with solar keratoses. Glucose-6-phosphate dehydrogenase (G6PDH) epidermal total activities were increased in both lesional and paralesional skin compared with buttock epidermis in all patients. In all skin samples G6PDH activity was preferentially increased in the granular cell layer. Lactate dehydrogenase (LDH) activity did not show a difference in localization in any tissues studied. When buttock skin of five healthy subjects was irradiated 10x during a 14-day period with 1-2 minimum erythemal doses of 290-400 nanometer, UV irradiation, SDH activity dropped approx 50% in the granular skin layer, but was unchanged in basal layer and total activities. Additonally, G6PDH activity increased significantly in the total epidermis and basal cell layer and somewhat in the granular cell layer after irradiation. It is suggested that these findings may serve as a model for persistent UV light exposure leading to epidermal damage in man. (2 refs)

78-6814 **Experimentally Induced Intestinal Metapla in Wistar Rats by X-Ray Irradiation.** (E Watanabe, H. (Dept. Cancer Res., Res. Inst. Nuclear Me cine and Biology, Hiroshima Univ., Kasumi 1-2-3, Hi shima, 734, Japan). *Gastroenterology* 75(5): 796-799; 197

The induction of intestinal metaplasia with Paneth cells a intestinal marker enzymes in Wistar rats by local x-irrad tion is described. The gastric region of 5-wk-old female W star rats was irradiated daily with 500 rads of x-rays up a total of six times. Goblet cells and marker enzymes of small intestine, such as lactase, trehalase, and maltase, peared in the pyloric region of the glandular stomach of rats from the first week after final irradiation. Intestinal-ty crypts without Paneth cells were observed at 8 wk, sucr activity at 26 wk, and intestinal metaplasia with Paneth c at 71 wk. The number of goblet cells, intestinal type cryp and Paneth cells increased with age. Gastric adenocarcino did not develop after irradiation. These studies suggest th a small dose of carcinogen might cause only intestinal me plasia and that increasing the dose level might result in c cinoma associated with metaplasia or, in the case of hea doses, carcinoma alone. (26 refs)

78-6815 **Acute Myelomonocytic Leukemia after Irrad tion and Chemotherapy for Ewing's Sarcor** (Eng) Smithson, W. A. (Dept. Pediatrics, Mayo Clinic, Ro ester, MN); Burgert, E. O.; Childs, D. S.; Hoagland, H. *Mayo Clin Proc* 53(11): 757-759; 1978.

A 16-yr-old boy was diagnosed with acute myelomonocy leukemia 16 mo after the start of irradiation and chemothe py for Ewing's sarcoma of the upper right leg. The prima lesion was treated with a daily midplane dose of 200 rads x-rays for 25 sessions over 29 days (total, 5,000 rads). Beg ning at the same time, vincristine (VCR: 2 mg/m², max d 2.0 mg) and cyclophosphamide (CP: 500 mg/m²) were giv weekly for 10 wk, followed by a 4-wk rest period. Then d tinomycin (0.015 mg/kg/day) was given for 5 days, follow by resumption of the weekly VCR and CP therapy for 5 w Four cycles of triple-agent chemotherapy were administere Fourteen months after the initial presentation, a portion the right lung involved by metastatic disease was resecte and the lungs were treated with a total of 1,800 rads of x-ra in 12 fractions over 16 days. Simultaneously, doxorubic (DR: 30 mg/m²/day) was given for 3 days and repeated on in 3 wk. Two months after the lung resection, the Hb le decreased and undifferentiated blasts appeared in the pe pheral blood; the total WBC count was 2,500/mm³ with 1 blasts. DR therapy was continued for 3 mo, at which tir the percentage of blasts increased to 38% of a total WB count of 40,000/mm³. At death, there was no clinical e dence for active Ewing's sarcoma. Although nothing in th case report suggests the need to modify the current approa to Ewing's sarcoma, it does signal the need for surveillan for second neoplasms of all types. (21 refs)

-6816 **Otolaryngolic Sequelae of Radiation Therapy.** (Eng) Kupperman, G. L. (Univ. Massachusetts, nherst, MA); Kleiner, H.; Stageman, D. L.; Martinelli, D. *r Nose Throat J* 57(11): 510-515; 1978.

e ears, nose, throat, and hearing of 100 persons who had en exposed to head, neck, or chest irradiation at least 10 previously were examined in an attempt to document the g-term effects of radiation treatment. There was no evi- ice of clinical carcinoma in the ear, nose, or throat struc- es of any of the patients. Temporomandibular-joint disease s found in three patients without the common historical physical findings usually found. One patient had bilateral argement of the submaxillary glands and two had unilater- enlargement. Few cases of conductive hearing loss or mid- -ear disease were observed. Nine of 27 patients with sen- ineural hearing loss gave no history of excessive noise posure or ototoxic drug therapy. The uncommonly high mber of patients with this type of hearing loss indicates ere may be some relationship to previous irradiation. (16 s)

-6817 **Effect of Some Nonradioactive and Radioactive Chemicals on Spleen Structure.** (Rus) nomareva, T. V. (Res. Inst. Radiation Hygiene, Lenin- ad, USSR); Merkushev, G. N. *Arkh Anat Gistol Embriol* (4): 47-52; 1978.

evaluate the effect of common environmental pollutants spleen structure, mice and rats received a series of radioac- e (^{137}Cs, ^{226}Ra, ^{89}Sr, ^{65}Zn) and nonradioactive [$Pb(NO_3)_2$, Cl_2] nuclides, hexamethylenediamine (HMDA), and chlo- methylmercury (CMM) in their drinking water for 1-2 yr. e compounds were given in concentrations (slightly great- than av and max permissible doses). Chronic exposure to and ^{225}Ra (total absorbed dose 0.3 and 5.4 rads, respec- ely), HMDA, and CMM enhanced cell proliferation in the d pulp. Structural rearrangement of the spleen tissue was companied by hyperplasia of the lymphoid tissue. Hyper- asia of the hematopoietic stem cells and enhanced plasma ll proliferation were detected after exposure of the rodents ^{226}Ra, ^{89}Sr, ^{65}Zn, and $BeCl_2$. At the end of experiment, the imals had a marked decrease in immune reactivity that incided with aplasia of the lymphatic component of the leen. (17 refs)

3-6818 **On the Mechanism of "Dissolution" in Liquids of PuO_2 by Alpha Decay.** (Eng) Fleischer, R. (General Electric Res. and Development Center, Schenec- dy, NY, 12301); Raabe, O. G. *Health Phys* 35(4):545-548; 978.

ubparticle formation by alpha decay of plutonium-239 in utonium oxide particles was studied by the nuclear track chnique to locate the sites of deposition of fissionable atoms or groups of atoms. Fission was induced on a high-purity quartz detector by thermal neutrons, and the individual tracks were revealed by chemical etching. Analysis of the results indicated that in a vacuum, at the most, a single ^{239}Pu atom was ejected with the uranium-235 recoil nucleus. Therefore, direct spraying-out of multiatom fragments does not occur. The most plausible model of the previously observed subparticle formation in water is that a damaged region is produced in the original particle and that the damage is subsequently released by exposure to water. (10 refs)

78-6819 **A Morphometric Study of Inhaled $^{239}PuO_2$ in Rodents (Meeting Abstract).** (Eng) Rhoads, K. (Battelle, Pacific Northwest Lab., Richland, WA, 99352); Sanders, C. L. *Pharmacologist* 20(3): 276; 1978. (no refs)

78-6820 **Toxicology of Inhaled Transuranic Oxides in Rodents (Meeting Abstract).** (Eng) Sanders, C. L. (Battelle, Pacific Northwest Lab., Richland, WA, 99352); Mahaffey, J. A. *Pharmacologist* 20(3): 175; 1978. (no refs)

78-6821 **Estimation of Risk for Lung Cancer Induced by Inhaled Alpha Emitting Radionuclides (Meeting Abstract).** (Eng) Mahaffey, J. A. (Battelle, Pacific Northwest Lab., Richland, WA, 99352); Sanders, C. L. *Pharmacologist* 20(3): 175; 1978. (no refs)

78-6822 **Factors Affecting the Mobility of Plutonium-238 Dioxide in the Rat.** (Eng) Stradling, G. N. (Natl. Radiological Protection Board, Harwell, Didcot, Oxon, England); Ham, G. J.; Smith, H.; Cooper, J.; Breadmore, S. E. *Int J Radiat Biol* 34(1): 37-47; 1978.

A major factor influencing the movement of plutonium-238 from lungs to blood after the administration of oxide suspensions to female inbred rats via intubation was the presence of 0.001-μm-diameter particles. In a polydisperse suspension of particles, this fraction increased with time, probably because of fragmentation of larger particles induced by alpha decay. The rate of this process could account for the greater transportability in vivo of plutonium-238 relative to plutonium-239 when the oxides were inhaled. In blood, 0.001-μm-diameter plutonium-238 oxide particles underwent a rapid reaction to form a low-mol-wt species before plutonium was complexed with transferrin and citrate ions. The filtration of this species through the kidneys may explain the observed enhanced urinary excretion of plutonium relative to administered plutonium citrate. The mechanism of urinary excretion and the relationship between cumulative urinary excretion and body content for plutonium-238 were similar to those

previously observed for plutonium-239, even though different methods of preparation of the oxides were used (calcination of the oxalate, $^{238}PuO_2$; condensation of the metal vapor, $^{239}PuO_2$). (25 refs.)

78-6823 **Studies on the Uptake of Plutonium from Major Indian Soils and Its Distribution in Plants.** (Eng) Vyas, B. N. (Biology and Agricultural Div., Bhabha Atomic Res. Centre, Trombay, Bombay 400 085, India); Mistry, K. B. *J Environ Qual* 7(4): 533-536; 1978.

Studies of the plant uptake of plutonium from three major Indian soil types showed that the highest amount of Pu was absorbed from acidic laterite soil, followed by alluvial soil and medium-black alkaline soil. Pu concentration ratios in beans and maize ranged from 1.5 to 9.6 x 10^{-4} for aerial tissues and from 13.9 to 15.3 x 10^{-4} for roots. In mature bean plants, the Pu distribution showed a marked acropetal gradient. (19 refs)

78-6824 **Size Fractionation Methods: Measuring Plutonium in Respirable Dust.** (Eng) Hayden, J. A. (Rockwell International, Rocky Flats Plant, P.O. Box 464, Golden, CO, 80401). *Science* 202(4369): 753-754; 1978.

Four soil fractionation methods were used to separate three size fractions of two soil samples in order to evaluate the inhalation hazard of soil contaminated with plutonium. Increasing amounts of soil mass and Pu activity (0.5%-38% and 7%-84%, respectively) remained in the soil fraction <10 μm. The two samples showed similar trends in the changing Pu content of this fraction, the change being highly dependent on the fractionation method used. (5 refs)

78-6825 **Influence of Injected Mass of Plutonium on Its Biological Distribution.** (Eng) Guilmette, R. A. (Inhalation Toxicology Res. Inst., P.O. Box 5890, Albuquerque, NM, 87115); Lindenbaum, A.; Friedman, A.; Sullivan, J.; Moretti, E.; Russell, J. J. *Health Phys* 35(4): 529-536; 1978.

The distribution and retention in mouse tissues of an injected mass of plutonium were investigated using four α-emitting Pu isotopes of differing specific activities: ^{236}Pu (532 μCi/μg Pu), ^{239}Pu (0.0613 μCi/μg), ^{242}Pu (0.0039 μCi/μg), and ^{244}Pu (1.93 x 10^{-5} μCi/μg). Female B6CF$_1$/Anl mice 88 days old, were injected iv with 1 μCi/kg of ^{236}Pu, ^{239}Pu, ^{242}Pu, or 0.3 μCi/kg of ^{244}Pu. Groups of five animals receiving each isotope were sacrificed 4-96 days after injection, and the following tissues were analyzed radiochemically by α-liquid scintillation counting for Pu content: liver, spleen, kidneys, lungs, lymph nodes, thigh muscle, ovaries, femurs, and tibias (marrow samples from both tibias were analyzed). In all the tissues analyzed, the early distribution and retention of ^{236}Pu, which was injected at a mass level (2 nanograms/kg) equ lent to 20% of the max permissible body burden (MPBB ^{239}Pu, did not differ from those of ^{239}Pu, even though injected masses differed by > 8,000. Retention of the isot of lower specific activity, ^{242}Pu and ^{244}Pu, which were inje at mass equivalents of 28,000 and 99,000 times the MI of ^{239}Pu, respectively, was generally three to six times hi than retention of ^{236}Pu and ^{239}Pu in the soft tissues. T results suggest the occurrence of an aggregation of ^{242}Pu ^{244}Pu in vivo. They also suggest that the use of metabolic obtained in animal studies with high levels of injected sol ^{239}Pu allows valid extrapolation downward to at least the l of an MPBB exposure. (13 refs)

78-6826 **Radiation Leukemia in C57BL/6 Mice. Correlation of Altered Expression of Term Deoxynucleotidyl Transferase to Induction of Leuke** (Eng) Pazmino, N. H. (Cancer Biology Program, N Frederick Cancer Res. Center, Frederick, MD, 21501); M wan, R.; Ihle, J. N. *J Exp Med* 148(5): 1338-1350; 197

In a study of the effects of irradiation on early thymo differentiation, terminal deoxynucleotidyl transferase (T activity was measured in C57BL/c mice irradiated with rads x-rays 1, 3, or 4 x/wk, beginning at age 1 mo. E radiation schedule resulted in a 60%-80% loss of thymoc at 1 wk post-treatment, but the subsequent repopulatio the thymus was dose lependent. Peak TdT I and II activ (expressed as percentage of nonirradiated controls) in thy and bone marrow decreased dramatically after a si 175-rad irradiation, but they returned to normal value 4 wk. Recovery of thymus TdT activity after two or t 175-rad doses took longer, and in the bone marrow there only 50% recovery. Four doses reduced activity to undete ble levels, and no TdT was detected in bone marrow fo least 18 wk. Radiation-induced thymic lymphomas in C5 mice were TdT-positive; high levels of thymus TdT acti were detectable only in overtly leukemic mice, regardles the time after irradiation. Bone marrow-reconstitution mediately after the last radiation abrogated the leukemic fect, and TdT levels were normal 6 wk after reconstitut Studies of the effects of 4 x 175 rads on mice of various showed that susceptibility to leukemia induction and ab to recover normal TdT activity were age-dependent. TdT tivity was induced in bone marrow B cells from thyme mized mice given a nonleukemic radiation dose (1 x 350 r but not in B cells from mice given 4 x 175 rads. This indic that a leukemogenic radiation dose eliminates or alters bone marrow stem cell population inducible for TdT. S the loss of the TdT stem cell was thymus-independent, primary effect of irradiation occurs in the bone marrow. refs)

78-6827 **Chronic Myelogenous Leukemia Develop After Thymic Irradiation.** (Eng) Shimaoka,

Medicine B, Roswell Park Memorial Inst., Buffalo, Sokal, J. E. *In: Third International Symposium on the ion and Prevention of Cancer held by the International Group for the Prevention and Detection of Cancer in ork, April 26-May 1, 1976.* International Study Group Prevention and Detection of Cancer (New York, NY): (part 1): 1193 pp; 819-830; 1977.

atients with Philadelphia (Ph′) chromosome-positive ic myelogenous leukemia (CML) and a history of thym- adiation are presented. The first patient underwent c irradiation for breathing difficulties and a widened or mediastinum on chest x-ray at 3 mo of age. Three of 100 rads in air were given every other day, for a total rads. He developed leukemia 18 yr later; chromosome is revealed 46XY with a single Ph′ chromosome in all hases prior to the blastic stage, after which 47XY with h′ chromosomes gradually became the sole karyotype. econd patient was given three doses/wk of 132 rads in an enlarged thymus at the age of 2 mo, for a total dose rads. Leukemia developed at the age of 22 yr; blast karyotyping revealed a mode of 45 chromosomes (a on of one of the Group C chromosomes) and a single romosome in all metaphases. It is concluded that both ts had radiation-induced CML. (39 refs)

28 **Behaviour of Murine Lymphosarcoma Cells During Prolonged Cultivation In Vivo.** (Eng) kova, V. (Inst. Biophysics, Czechoslovak Acad. es, Brno 12, Czechoslovakia); Drasil, V. *Folia Biol a)* 24(4): 253-263; 1978.

nsplantable lymphosarcoma growing as a free suspen- n the peritoneal cavity of isologous hosts was isolated fractionated irradiation of C57BL mice (4 x 160 R at intervals). During a 14-yr cultivation period, the modal er of tumor chromosomes declined from 41-42 to 39, ean survival time of tumor hosts decreased, and the esistance of the tumor cells increased slightly. Strain icity remained unchanged. (25 refs)

29 **Estimation of Life Shortening Resulting from Radiogenic Cancer per rem of Absorbed Dose.** Gotchy, R. L. (Radiological Assessment Branch, U.S. ar Regulatory Commission, Washington, DC, 20555). *h Phys* 35(4): 563-565; 1978.

mount of life shortening (LS) from the cancer that may pected from a radiation dose equivalent to 1 rem (roent- quivalent-man) was estimated. Equations are given for mining the LS for a given age cohort. The av LS for each f cancer death was estimated by summing all the years r each age cohort over the entire population. The total sociated with all cancer types for total body irradiation opulation was derived from the sums of av LS by cancer type. The total LS per million man-rem is 3,200 yr for the general public. The av loss of life expectancy per individual is 1.2 days/rem. An upper-bound estimate of the av LS of radiation workers per 5-rem dose equivalent was calculated using the 20- to 70-yr population. The av loss of life expectancy for this group for all types of cancer was calculated as 0.63 day/man-rem. It is believed, however, that the actual age distribution of nuclear workers may be skewed toward the younger years. Therefore, the LS of occupationally exposed radiation workers in the nuclear industry is expected to lie between 0.63 and 1.2 days/rem. (4 refs)

78-6830 **Late Effects after Incorporation of the Short-lived α-Emitters ^{224}Ra and ^{227}Th in Mice.** (Eng) Muller, W. A. (Institut fur Biologie Gesellschaft fur Strahlen- und Umweltforschung mbH, D-8042 Neuherberg, W. Germany); Gossner, W.; Hug, O.; Luz, A. *Health Phys* 35(1): 33-35; 1978.

Dose dependence and temporal distribution of osteosarcomas (OS's) and other malignancies were investigated following single and repeated ip injections of ^{224}Ra of varying activity and single injections of ^{227}Th in NMRI mice. The highest concentration of ^{224}Ra occurred in the long bones, followed by the vertebral column, especially the lumbar spine. After a single injection of ^{224}Ra (1.0-50 μCi/kg, 30-1,500 rads), the OS incidence ranged from 7% to 22% (at 360 rads) in females vs 1.3% in controls. Males had a max incidence of 8.5% at 750 rads (dose range, 5-50 μCi/kg, 150-1,500 rads) vs 0% in controls. A single injection of ^{227}Th in females produced a max incidence of 60% at 1,000 rads. Fractionated application of ^{224}Ra resulted in a higher overall incidence of OS than that from a single injection of the same mean skeletal dose. The highest tumor incidence (> 90%) was observed with the lowest activity per injection, 0.5 μCi/kg 2 x/wk for 36 wk (total, 1,080 rads). Tumor incidence was also increased when the same mean skeletal dose was distributed over a longer treatment period. When 0.5 μCi/kg was given 2 x/wk for 36 wk, a 92% OS incidence resulted at 17 mo, but 0.5 μCi/kg 2 x/wk for 12 wk resulted in only a 46% incidence at 23 mo. OS's occurring with single-dose treatments at the higher doses were located mainly in the head bones; these treatments also increased the incidence of ossified fibromas. Fractionated doses and lower single doses generally produced osteosarcomas in sites other than the head. An earlier occurrence of leukemia was seen in some ^{227}Th-treated groups and in one group given repeated ^{224}Ra injections. (34 refs)

78-6831 **Toxic Autonomous Thyroid Nodule Following Neck Irradiation.** (Eng) Scott, R. S. (Medical Unit, Princess Margaret Hosp., Christchurch, New Zealand); Brownlie, B. E.; Bremner, J. M. *Aust NZ J Med* 8(5): 521-522; 1978.

A 37-yr-old man with history of neck irradiation in childhood

presented with thyrotoxicosis due to an autonomous thyroid nodule. Adjacent to the nodule was a radiation scar from radiotherapy administered 35 yr previously. The long latent period is not unusual, in that thyroid abnormalities have been observed >30 yr after radiation. Hemithyroidectomy was performed, and histological examination excluded malignant change. (6 refs)

78-6832 **Radiation Induced Cancer in the Head and Neck Region.** (Eng) Matsumura, Y. (Div. Head and Neck Surgery, Natl. Kyushu Cancer Center, Fukuoka, Japan); Nomura, Y.; Eguchi, S.; Horie, A. *In: Third International Symposium on the Detection and Prevention of Cancer held by the International Study Group for the Prevention and Detection of Cancer in New York, April 26-May 1, 1976.* International Study Group for the Prevention and Detection of Cancer (New York, NY): Vol. 1(part 1): 1193 pp.; 807-818; 1977.

Twelve patients with radiation-induced cancer, 8 initially treated for benign conditions (Group A) and 4 initially treated for malignant tumors (Group B), were analyzed. The primary tumors in the latter group were reticulum cell sarcoma of the maxilla, squamous cell carcinoma of the larynx (2), and nasopharyngeal carcinoma. At the time of therapy, the av age of the Group A patients was 19 yr, that of the Group B patients 44 yr. However, the mean latent interval for Group A was 33 yr, vs only 13 yr for Group B; no cancer developed <7 yr after the initiation of radiation therapy. Although the radiation dose was not known for some patients, it was estimated that those in Group A received 2,000-5,000 rads, those in Group B 6,000-8,000 rads. Damage to the head and neck skin in Group A patients included fibrosis, stigma, irregular pigmentation, and leukoderma, but Group B patients had only a slight dermatosis. The difference in damage is suggested to be due to the radiation dose, source, and field. Histologically, the radiation-induced cancers were generally anaplastic. They spread diffusely and were of uniform thickness. The radiation-induced cancers are proposed to arise by the two-stage mechanism. The possibility of cancer developing in irradiated patients after a certain latent interval is distinct; these patients should be monitored carefully. (23 refs)

78-6833 **Contamination of the Home Environment by Patients Treated with Iodine-131: Initial Results.** (Eng) Jacobson, A. P. (Dept. Environmental and Industrial Health, Univ. Michigan Sch. Public Health, Ann Arbor, MI, 48109); Plato, P. A.; Toeroek, D. *Am J Public Health* 68(3): 225-230; 1978.

Twin-sodium iodide-radiation detectors were used to analyze iodine-131 transfer from thyroid patients to their families. The study included seven families with 17 persons, 11 of whom were under age 16. Direct radiation exposure of family members due to the proximity of the radioactive patients ranged from 0.17 to 126 mR/day (natural background radi tion is 0.35 mR/day). The range of max activity of iodine-1 in the thyroids was 92-110,000 picocuries, and it resulted thyroid dose equivalents of 4-1,330 milliroentgen-equiv lent-man. Based on recent estimates of thyroid cancer, t latter dose equivalent could double the risk of thyroid mali nancy in children over what is expected normally. Such a ri implies the addition of 10 induced cases to the 10 natural occurring cases per million people per year. (20 refs)

78-6834 **Fate of Inhaled Transuranic Oxides (Meeti Abstract).** (Eng) Adee, R. R. (Battelle, Pacif Northwest Lab., Richland, WA, 99352); Sanders, C. L.; Ha ley, J. G. *Pharmacologist* 20(3): 276; 1978. (no refs)

78-6835 **Development of Osteosarcoma in Rats After I radiation.** (Eng) Solheim, O. P. (Norsk Hydro Inst. Cancer Res., Oslo, Norway). *Acta Radiol [The (Stockh)* 16(5): 433-446; 1977.

Tissue abnormalities preceding the development of osteoge ic sarcoma were determined in inbred male rats exposed ^{90}Sr (in equilibrium with its daughter isotope ^{90}Y) radiatio with activities of 0, 0.05, 0.2, 0.67, or 1.32 μCi/cm. The an mals were exposed to the radiation for various times rangi from 4 to 360 days and then sacrificed at times ranging fro 4 to 540 days. In the medullary cavity, the main effect of t irradiation was a slow and dose-dependent replacement of t hematopoietic elements by fat. Neither extensive fibrosis n irregular nontumorous bone was found in the marrow cavi of any animal exposed to continuous irradiation. After term nation of irradiation, the hematopoietic tissue was reforme In the cortical bone, the number of osteocytes decreased a dose-dependent rate; this decrease continued after t radiation was discontinued. Osteoclasts were found on t periosteal surface of all bones exposed for 14-45 days b they were rarely found on the endosteal surface. The end steal surfaces were always lined by resting osteoblasts aft exposure to at least 0.42 Gray unit/day (all groups above 0.0 μCi/cm). A total of 22 tumors were noted: 4 in the 0.2-, in the 0.67-, and 12 in the 1.32-μCi/cm groups. Nineteen these tumors were sarcomas and 10 were osteogenic sa comas. Malignant proliferation began after approx 180 da of irradiation. Osteogenic sarcomas had their centers at t endosteal surface. The adjacent bone marrow was near aplastic, but the endosteum was thickened by fibroblasts an osteoblasts. The number of osteocytes in the adjacent bon was greatly reduced. It is suggested that radiation injury a cumulated in osteogenic cells until some mechansism i volved in the control of proliferation and differentiatio failed. (7 refs)

78-6836 **Preliminary Studies of the In Vitro Cellular E fects of Asbestos and Fine Glass Dusts.** (Eng Sincock, A. M. (Dept. Human Genetics and Biometry, Univ

London, London NW1 2HE, England). *In: Mechanisms rcinogenesis. Proceedings of the Cold Spring Harbor Con-ces on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; ten, J. A., eds. (Cold Spring Harbor: Cold Spring Har-aboratory): Origins of Human Cancer. Vol. 4 (Book B), p.; 941-954; 1977.

se hamster cells that had been cloned from a single line cell and checked for a total modal variation of were incubated with various samples of asbestos (0.1 ml) for 48 hr and then subjected to genetic analysis. With f the asbestos samples (S.F.A. chrysotile and U.I.C.C. dolite), there was a high level of aberration, with > 50% cells analyzed being karyotypically abnormal. The oth-estos samples also showed significant levels of genetic rmality. No significant genetic damage was observed in res treated with coarse fiberglass. A fine glass fiber sam-ode 100), which contained fibers within the diameter ength ranges of asbestos, also produced a significant of aberration in treated cells. Both chemical leaching nechanical milling of asbestos fibers significantly re-l the ability of asbestos to induce in vitro genetic dam-These results indicate the importance of physical mor-gy in the induction of genetic damage by asbestos. They ndicate that this system could be used to grade fine dusts e basis of induced genetic aberration. (10 refs)

837 **Malignant Mesothelioma Arising after Direct Application of Asbestos and Fiber Glass to the ardium.** (Eng) Churg, A. (Dept. Pathology, Sch. Medi-Univ. California, San Francisco, CA, 94143); Warnock, .; Bensch, K. G. *Am Rev Respir Dis* 118(2): 419-424;

-yr-old man developed a malignant mesothelioma 15 yr he had been treated for angina pectoris by dusting of ericardial cavity with a mixture of fibrous dusts. Elec-diffraction and microprobe analysis indicated that ap-67% of the fibers were tremolite and anthophyllite as-s and the remainder were fiber glass. This is believed to e first human malignant mesothelioma associated with t mesothelial contact with fibrous dusts. (14 refs)

838 **Mortality after Long Exposure to Cummingto-nite-Grunerite.** (Eng) McDonald, J. C. (TUC enary Inst. Occupational Health, London Sch. Hygiene and Tropical Medicine, Keppel St., Gower St., London WC 1, England); Gibbs, G. W.; Liddell, F. D.; McDonald, A. D. *Am Rev Respir Dis* 118(2): 271-277; 1978.

The causes of death of 657/660 former cummingtonite-grunerite workers were investigated to determine if exposure to these minerals carried an increased risk of respiratory tract cancer. Excess mortality with a clear dust-exposure relationship was found for pneumoconiosis and respiratory tuberculosis, but there was no convincing evidence of an increase in respiratory cancer. (9 refs)

78-6839 **Inhalation Studies with Polyurethane Foam Dust in Relation to Respiratory Tract Carcinogenesis.** (Eng) Thyssen, J. (Institut fur Toxikologie der BAYER AG, 5600 Wuppertal 1, W. Germany); Kimmerle, G.; Dickhaus, S.; Emminger, E.; Mohr, U. *J Environ Pathol Toxicol* 1(4): 501-508; 1978.

Male and female Sprague-Dawley rats inhaled freshly generated polyurethane foam dusts (8.65 mg/m^3 air) for 6 hr/day, 5 days/wk, over a 12-wk period. The exposure had no apparent effect on appearance, behavior, body wt, or life-span, and there were no indications of a carcinogenic effect of the dusts on the respiratory tract. (11 refs)

See also:
*(Rev.): 78-6609, 78-6612, 78-6614, 78-6620, 78-6624, 78-6633, 78-6634, 78-6665, 78-6666, 78-6667, 78-6668, 78-6697, 78-6704.
*(Chem.): 78-6753, 78-6759, 78-6765, 78-6777, 78-6792.
*(Viral): 78-6941, 78-6947.
*(Immun.): 78-6979, 78-7061.
*(Path.): 78-7072, 78-7090, 78-7091, 78-7092, 78-7102, 78-7121.
*(Epid.-Biom.): 78-7155, 78-7170, 78-7171, 78-7179, 78-7182.

78-6840 **Cell-free Translation of Avian Sarcoma Virus RNA: Suppression of the *gag* Termination Codon Does Not Augment Synthesis of the Joint *gag/pol* Product.** (Eng) Weiss, S. R. (Dept. Microbiology, Univ. California, San Francisco, CA, 94143); Hackett, P. B.; Oppermann, H.; Ullrich, A.; Levintow, L.; Bishop, J. M. *Cell* 15(2): 607-614; 1978.

The effect of yeast suppressor transfer RNA's (tRNA's) on the cell-free translation of two viral gene products (Pr76*gag* and P180*gag/pol*) from the 38S messenger RNA (mRNA) of avian sarcoma virus (ASV) was studied. Although the synthesis of P180*gag/pol* was not enhanced by the suppressor tRNA's, and the use of amber suppressor tRNA reduced the synthesis of Pr76*gag* and resulted in the synthesis of a new 80,000-dalton polypeptide (P80) that contained the antigenic determinants of *gag*. Studies using chemical inhibitors of the initiation of translation demonstrated that P80 was generated by the addition of amino acids to the carboxy terminus of Pr76. The data indicate that the ASV *gag* gene is terminated by an amber codon, UAG, and that suppression of this termination signal does not lead to uninterrupted translation from *pol*. A second termination signal about 120 nucleotides from the UAG termination appears to define the length of P80. Thus, at least two suppression events would be necessary to synthesize $P180_1$. This argues against the hypothesis that suppression of nonsense codon(s) at the end of the *gag* gene is responsible for the synthesis of $P180_1$ in the ASV-infected cell. (28 refs)

78-6841 **Characterization of Transformation-Sensitive Membrane-Proteins in Chick Embryo Fibroblasts Transformed with Avian Sarcoma Virus.** (Eng) Isaka, T. (Dept. Viral Oncology, Cancer Inst., Kami-Ikebukuro, Toshima-ku, Tokyo 170, Japan); Ikawa, Y.; Yoshida, M. *Virology* 90(2): 330-343; 1978.

A membrane polypeptide of 90,000 daltons (P90) found in increased amounts of chick embryo fibroblasts transformed by avian sarcoma virus was characterized, and its accumulation in transformed cells was studied. Compared with normal cells, there was a marked increase in the amount of P90, some increase in P79, and a decrease in P200 in transformed cells. Autoradiography showed that P90 had exactly the same isoelectric point as a polypeptide of 91,000 daltons (P91). Comparison of the peptide maps of P90 and P91 showed that the two polypeptides had very similar primary structures. P91 was shown not to be a glycoprotein, and it appeared to be the glycosylated form of P90. However, there was no conversion of P91 to P90 by deglycosylation. It is concluded that P91 is formed by glycosylation of the growing polypeptide P90 on polysomes, that P90 is formed in the absence of gly sylation, and that the completed polypeptides are not in convertible. (26 refs)

78-6842 **A Simple Method for Rapid Purification of A an Sarcoma Virus Supercoiled DNA by Se tive Precipitation of Infected Cell Chromatin.** (Eng) G taka, R. V. (Dept Microbiology, Coll. Physicians Surgeons, Columbia Univ., New York, NY, 10032). *Anal ochem* 90(1): 256-261; 1978.

A simple and effective method of partially purifying av sarcoma virus (ASV) supercoiled (form I) DNA from inf ed quail tumor cells (QT6) consists of lysing infected nuclei in water and precipitating the resulting chromatin w sodium chloride. This method offers some advantages o the Hirt procedure in that low-mol-wt viral DNA can extracted rapidly and only 1%-2% cellular DNA is fo in the viral fraction, even when the total number of cell be processed is as high as 3-4 x 10^9. The total amoun ASV-specific DNA recovered was 70%-100% of that re ered by the Hirt method. Similar results were obtained w simian virus 40 (SV40)-infected cells were processed by two methods, with the chromatin method extracting ab 85% of the SV40 DNA extracted by the Hirt procedure. efficiency of the two methods was compared by monito the recovery of ASV DNA after final purification. App 3 x 10^9 QT6 cells were labeled with ^{3}H-thymidine immedi ly after ASV infection. The nuclei were prepared and divi into two parts, and each half was subjected to one of purification procedures. Complete purification of ASV f I DNA, as monitored by alkali sucrose gradient analysis quired only two steps by the chromatin method, whereas least three or four steps, including two CsCl-propidium d cide equilibrium gradient centrifugation steps were requ to eliminate contaminating cellular DNA in the Hirt su natant. Because of the extremely low levels of host cell D in the postchromatin fraction, the method is particularly s able for purifying low-mol-wt viral DNA's, such as R tumor virus and SV40 DNA's. (6 refs)

78-6843 ***env* Gene of Chicken RNA Tumor Viruses: tent of Conservation in Cellular and V Genomes.** (Eng) Fujita, D. J. (Cancer Res. Lab., Univ. W ern Ontario, London, N6A 5B7 Ontario, Canada); Tal Varmus, H. E.; Bishop, J. M. *J Virol* 27(3): 465-474; 19

Molecular hybridization studies with DNA complemen to *env* gene sequences of chicken leukosis-sarcoma v

's (cDNA) were performed with a variety of avian s to examine the natural distribution and possible ori- f viral *env* genes. The results indicate that nucleotide nces closely related to cDNA are present in chicken but not in other avian DNA's tested or in calf thymus almon sperm DNA's. These results are in marked con- o experience with the transforming gene (*scr*) of avian ma viruses, for which homologs have been demonstrat- the DNA's of all avian species tested and also in the 's of other vertebrates. The *env* gene sequences were to be present in the DNAs of both chick helper fac- sitive and chick helper factor-negative (chf-) chicken t a level of one copy per haploid genome. The presence v gene sequences in chf- DNA suggests that the chf- otype does not result from a major deletion of *env* gene nces, and it is consistent with the existence of mech- s for the regulation of *env* gene expression. Thermal uration studies were used to further examine the logy between the *env* genes of representatives of viral oups A to E. The results indicate that the hybrids d between cDNA and RNA's of subgroup A to E s are closely matched. This suggests that a substantial n of the *env* genes of viruses of subgroups A to E con- f shared, closely related sequences and that these genes bly have a common evolutionary origin. (36 refs.)

844 **Isolation and Characterization of the Envelope Glycoprotein of an Avian Osteopetrosis Virus: t of Host Cell on Antigenic Reactivity.** (Eng) Van El- . J. (Rockefeller Univ., 1230 York Ave., New York, 10021); Smith, R. E. *Virology* 90(1): 80-89; 1978.

hysical and antigenic properties of the surface glyco- in (gp85) of avian myeloblastosis-associated virus V-2(O)] were compared with those of avian myeloblasto- rus (AMV) gp85. Sodium dodecyl sulfate-polyacryla- gel electrophoresis and guanidine hydrochloride col- chromatography indicated that the gp85's of the two s were qualitatively similar, but that MAV-2(O) con- d approx 3.46 times more gp85 than AMV. When the of MAV-2(O) grown in chick embryo fibroblasts (CEF) xamined by competition radioimmunoassay (RIA) us- abbit anti-AMV gp85 serum, it exhibited 100- to -fold less reactivity than the AMV glycoprotein. In con- MAV-2(O) isolated directly from the serum of osteope- chickens competed efficiently. If MAC-2(O)-infected n of osteopetrotic chickens was replicated in CEF for 1 t subsequently lost its ability to compete in RIA with . AMV itself did not compete effectively when grown EF, but it did so when grown in myeloblasts. MAV-2(O) ted from serum or CEF competed equally in RIA's using erum against B77 virus gp85, and glycoproteins from -grown MAV-2(O) and serum AMV showed equal ivity to the B77 antiserum. These results suggest MAV-2(O) and AMV gp85 show similar host- ndent glycosylation patterns in vivo and different erns when the viruses are grown in cultured CEF. efs)

78-6845 **Fractionation of Proteins from Rous Sarcoma Virus and Avian Myeloblastosis Virus by Isoelectric Focusing.** (Eng) Mach, O. (Inst Molecular Genetics, Czechoslovak Acad of Sciences, Prague 6, Czechoslovakia); Sovova, V.; Cerna, H. *Folia Biol (Praha)* 24(4): 233-241; 1978.

The technique of isoelectric focusing in pH gradients was used to isolate proteins from Rous sarcoma virus and avian myeloblastosis virus. The purified major group-specific (gs) protein p27 (pI = 9.1) and gp86 (pI = 5.3) were obtained after disruption of virus with 1% nonionogenic detergent in the presence of 6M urea. Proteins p10, p15, and p19 were present in the same pH range (pI = 6.8). A strongly basic, immunologically active protein, presumably p12, was found in the alkaline region at pH 10.8. These proteins fully retained their immunological activity. On the other hand, in the acidic region between pH 4 and 5, strong precipitates were regularly found. These precipitates were complexes that were formed by interaction of the acid components of ampholines with the viral proteins during isoelectric focusing. Almost all viral proteins were present, differing only in quantity. The complexes were stable in 1% nonionogenic detergent with 6M urea. They were dissociated with 1% sodium dodecyl sulfate and 5M urea, and they had no immunological activity. The methods of virus disruption and the possibility of formation of the ampholine-viral protein complexes are discussed. (23 refs)

78-6846 **Assay for Early Cytoplasmic Effects of the *src* Gene Product of Rous Sarcoma Virus.** (Eng) McClain, D. A. (Rockefeller Univ., New York, NY, 10021); Maness, P. F.; Edelman, G. M. *Proc Natl Acad Sci USA* 75(6): 2750-2754; 1978.

The *src* gene product of Rous sarcoma virus (RSV) was assayed by microinjection of cytoplasmic extracts of chick embryo fibroblasts transformed by the Prague strain of RSV (subgroup A) into normal mouse 3T3 fibroblasts and then examining the actin-containing structures in these cells by immunofluorescence microscopy. Microinjection of these cytoplasmic extracts, but not extracts of normal cells, caused a dissolution of the 3T3 cell microfilament bundles that was max within 30 min. The activity could still be measured after a tenfold dilution of the cytoplasmic extracts (14 mg/ml original protein concentration). The activity was trypsin-sensitive and it was destroyed by boiling, but it was not RNase-sensitive. Protein synthesis was not required for the dissolution. Microinjected cytoplasts prepared from normal 3T3 cells also dissolved the microfilament bundles, indicating that the cell nucleus was not required for expression of activity. Extracts made from fibroblasts transformed by RSV having a temperature-sensitive mutation in the *src* gene were also temperature-sensitive in this assay. Thus, the activity of extracts from cells infected with *src* mutant virus, but not from cells infected with wild-type virus, was destroyed either by in vitro incubation of the extract at the nonpermissive temperature before

injection or by incubation of recipient cells at the nonpermissive temperature after injection. It is concluded that the microinjection assay can detect a cytoplasmic activity coded for by the *src* gene RSV and that an early direct or indirect target of the *src* gene product is the cytoskeleton and cell motility system. This result is discussed in relation to the hypothesis that submembranous arrays of microfilaments, microtubules, and their associated proteins interact with cell-surface receptors to form a surface-modulating assembly that functions as a key regulator of cell growth. (13 refs)

78-6847 **Linkage of the Endogenous Avian Leukosis Virus Genome of Virus-producing Chicken Cells to Inhibitory Cellular DNA Sequences.** (Eng) Cooper, G. M. (Sidney Farber Cancer Inst., Dept. Pathology, Harvard Medical Sch., Boston, MA, 02115); Silverman, L. *Cell* 15(2): 573-577; 1978.

To account for the inefficient transcription and lack of infectivity of endogenous Rous-associated virus-O (RAV-O) DNA of uninfected virus-producing (V+) cells, it was proposed that the endogenous RAV-O genome was linked to a cis-acting control element of cellular DNA that inhibited its transcription. The prediction of this model that shearing the DNA of uninfected V+ cells might convert the endogenous RAV-O genome to an infectious form by separating it from the control element was tested. The DNA of uninfected V+ chicken cells was infectious at a low level. In addition, the infectivity of RAV-O DNA of uninfected V+ cells was increased approx sixfold by shearing the DNA to the approx size of the viral genome. In contrast, shearing the DNA of RAV-O-infected cells reduced its infectivity 5- to 20-fold. Thus, the infectivity of endogenous RAV-O DNA relative to the infectivity of DNA of RAV-O infected cells was increased approx 60-fold by shearing. These results suggest that the endogenous RAV-O genome of V+ chicken cells is linked to cellular DNA sequences that inhibit its infectivity in transfection assays, as predicted by the cis-acting control element model. Alternative interpretations, however, such as the possibility that shearing leads indirectly to internal rearrangements in the viral genome, cannot be excluded. Since the infectivity of sheared DNA of uninfected cells was approx 0.3% of the infectivity of sheared DNA of RAV-O-infected cells, the size of the control element was roughly estimated at 0.1%-1% in the size of the RAV-O genome, or 10-100 nucleotide base pairs. These findings suggest that the endogenous viral genome of uninfected V+ chicken cells is linked to specific inhibitory cellular DNA sequences, and they provide further evidence consistent with the model of endogenous viral gene regulation. (17 refs)

78-6848 **Evidence That the Transforming Gene of Avian Sarcoma Virus Encodes a Protein Kinase Associated with a Phosphoprotein.** (Eng) Levinson, A. D. (Dept. Microbiology, Univ. California, San Francisco, CA, 94143); Oppermann, H.; Levintow, L.; Varmus, H. E.; Bisl op, J. M. *Cell* 15(2): 561-572; 1978.

Immunoprecipitation with rabbit tumor antisera to avian sa coma virus (ASV) was used to isolate a phosphorylated pr tein of mol wt 60,000 daltons (pp60). This protein appear to be encoded by the *src* gene responsible for the inducti and maintenance of neoplastic transformation. Phosphoryl tion of pp60 could be accomplished in vitro with extracts ASV-infected cells. With a temperature-sensitive condition mutation in *src*, phosphorylation of the pp60 protein w temperature-sensitive. Since the mutant *src* was not expresse at the restrictive temperature, phosphorylation of pp60 m be required for its function as the putative effector of s Immunoprecipitates prepared with extracts of ASV-infect cells and the rabbit tumor antisera contained a protein kina activity that catalyzed phosphorylation of the heavy chai of immunoglobulin molecules, using either ATP or guanosi triphosphate as phosphate donor. It appears that the prote kinase may also be encoded in *src* and that the enzymat activity may be an intrinsic property of pp60. Phosphoryl tion of pp60 in cellular extracts was inhibited by calcium io whereas the immunoprecipitable kinase activity was not, su gesting that the kinase responsible for pp60 phosphorylati may be distinct from that encoded in *src*. The data sugge that phosphorylation of specific cellular targets may accou for transformation of the host cell by *src*. (36 refs)

78-6849 **Ascorbic Acid Retards RNA-Tumor Virus I fection of Avian Cells in Culture (Meeting A stract).** (Eng) Bissell, M. J. (Lab. Chemical Biodynami LBL, Univ. California, Berkeley, CA, 94720); Hatie, C.; Fa son, D.; Schwarz, R.; Soo, W. J. *J Cell Biol* 79(2, part 401a; 1978. (no refs)

78-6850 **Limited Host Range of Avian Tumor Viruses Pigeon Cells.** (Eng) Meyers, P. (Dept. Micro ology, Mayo Clinic and Mayo Medical Sch., Rochester, M 55901); Ritts, G. D.; Heise, J. M.; Qualtiere, L. F. *Virol* 90(1): 162-165; 1978.

Show Racer (SHR) and White Corneau (WC) pigeon embr fibroblasts (PEF) were found to be virtually resistant to inf tion with Rous sarcoma virus (RSV) of subgroups A, B, D, and E. Focus assays were performed on five SHR PE and six WC PEF cultures, using nine RSV strains, represe ing all five subgroups. PEF were absolutely resistant to su groups A and E and 2/3 subgroup B viruses. Schmidt-Rupp (SR)-RSV, subgroup B, plated to some degree on many e bryos, but its max plating efficiency (EOP) was 0.0002 re tive to standard chicken embryo fibroblasts (CEF). Subgro C viruses plated poorly, but SR-RSV, subgroup D, plated relatively high titers in several PEF, the max EOP being 0. relative to CEF. Although SHR is an outbred and WC inbred strain, there was little difference in PEF resistance RSV. (16 refs)

1 **Binding of Tryptophanyl-tRNA to the Reverse Transcriptase of Replication-defective Avian a Viruses.** (Eng) Panet, A. (Dept. Virology, Hebrew Hadassah Medical Sch., Jerusalem, Israel); Weil, G.; R. R. *J Virol* 28(2): 434-443; 1978.

NA polymerase activity and the binding to tryptopha- nsfer RNA of the reverse transcriptase (TR) from five onal avian sarcoma virus mutants, two (LA 335 and 5) carrying an early replication lesion and three (LA A 343, and LA 672) defective in a late replication n, were examined. Compared with the activities of the pe parents, both RT activities were found to be ther- e in LA 335 and LA 336. When the other mutant were grown at the permissive temperature, the RT es were nearly as heat-stable as those of the wild-type . At the nonpermissive temperature, however, both es were reduced in LA 338, LA 343, and LA 672. he relative amounts of RT antigen in these virions was ed by a competition immunoassay, it was found that e contained reduced amounts of RT protein per total roteins when harvested at the nonpermissive tempera- ven the infectious virus mutants produced at the per- temperature always contained less enzyme protein e wild-type parents. (27 refs)

52 **Characterization of Rous Sarcoma Virus *src* Gene Products Synthesized In Vitro.** (Eng) Bee- K. (Tumor Virology Lab., Salk Inst., San Diego, CA, ; Hunter, T. *J Virol* 28(2): 551-566; 1978.

ell-free translation products of Rous sarcoma virus virion RNA were further characterized by parallel tion of the heat-denatured virion RNA's of Prague up B (PR-B), Schmidt-Ruppin subgroup D (SR-D), ansformation-defective (td) SR-D RSV in the messen- NA-dependent reticulocyte lysate system. Two-dimen- analysis of the tryptic peptides of the 17,000 (17K), and 60K proteins synthesized by PR-B and SR-D but not td SR-D RNA, revealed that they have over- g amino acid sequences. However, these products d strain-specific differences, manifested by their elec- retic mobility in acrylamide gels and by their tryptic es. Virion RNA's coding for the 17K, 25K, and 60K ns were polyadenylated and they sedimented with max A activity at about 23S, 19S-20S, and 18S, respectively. formation-specific proteins with mol wts of 39K and ere also synthesized. These proteins were related to the three proteins, and were synthesized from polyadeny- RSV RNA of approx 21S-22S. RNase T_1-resistant ucleotides were analyzed in parallel, and the *src*-specif- onucleotides were found to be first present in equimolar nts in gradient fractions sedimenting at 21S-22S. The uggest that synthesis of the 60K protein is initiated near end of the *src* gene and that the 39K, 33K, and 17K proteins are initiated internally in the *src* gene. All these proteins appear to be initiated ini- tiated independently, but they may have a common termination site. (30 refs)

78-6853 **Study of Group-specific Proteins in Mammalian Cells Transformed by Rous Sarcoma Virus.** (Eng) Sovova, V. (Inst. Molecular Genetics, Czechoslovak Acad. Sciences, Praha 6, Czechoslovakia); Bosch, V.; Cerna, H. *Folia Biol (Praha)* 24(3): 199-205; 1978.

Lysates of rat, mouse, and hamster cells transformed by Rous sarcoma virus (RSV) and labeled with ^{35}S-methionine were examined for the presence of group-specific (gs) proteins by means of antisera, and the size of these molecules was deter- mined by gel electrophoresis. Gs proteins were not detected in any of the immunoprecipitates analyzed. Only in RSH-mix cells (Syrian hamster embryo fibroblasts transformed in vitro by the Schmidt-Ruppin strain of RSV) was there a quantita- tive difference in the amount of a 70,000-dalton protein. Au- toradiograms of simultaneously tested immunoprecipitates of lysates of RSV-transformed chicken cells clearly showed the presence of p27 and, after a short-term labeling period, the gs precursor molecule pr76. In previous experiments using complement fixation, gs proteins were detected in two of the RSV-transformed mammalian cell lines. The most probable explanation for this discrepancy is that the precursor mole- cule is attached to subcellular structures in mammalian tu- mor cells. (21 refs.)

78-6854 **Analysis of Rous Sarcoma Virus (RSV) RNA Structure by Means of Specific Nucleases.** (Eng) Darlix, J. L. (Departement de Biologie Moleculaire, Universite de Geneve, CH-1211-Geneve 4, Switzerland); Spahr, P. F.; Bromley, P. A. *Virology* 90(2): 317-329; 1978.

The effects of *Escherichia coli* RNases III and IV and *Aspergillus oryzae* T_1 ribonuclease and S1 nuclease on Rous sarcoma virus (RSV) 70S and 35S RNA were analyzed by the fingerprinting technique. The viral RNA was very susceptible to both RNases III and IV, with five regions being highly susceptible. Of these five regions, two, represented by T_1 oligonucleotides 13 and 2, are directly related to the initiation sites for reverse transcriptase. A large number of RSV RNA regions excluded from Sephadex G-75 were resistant to deg- radation by T_1 RNase, with 35S RNA being much less resist- ant than 70S RNA. Regions of 70S RNA with oligonucleo- tides 8, 15, and 9 were very resistant to S_1 nuclease; similar results were found with 35S RNA. Large T_1 oligonucleotides were not very susceptible to RNases III and IV, with the exception of oligonucleotides 2 and 18. The results indicate that RSV RNA is a highly structured molecule in which the two 35S subunits are intimately associated via a large number of specific interactions to form the 70S complex. (37 refs)

78-6855 **Fluorescent Probe Studies of Normal, Persistently Infected, Rous Sarcoma Virus-transformed, and Trypsinized Rat Cells.** (Eng) Burleson, G. R. (Lobound Lab., Dept. Microbiology, Univ. Notre Dame, Notre Dame, IN, 76556); Kulpa, C. F.; Edwards, H. E.; Thomas, J. K. *Exp Cell Res* 116(2): 291-300; 1978.

The fluorescent probes pyrene, pyrene butyric acid, and N-phenyl-1-naphthylamine were used to study membranes of normal rat cells, Rous sarcoma virus (RSV)-transformed cells, cells treated with a proteolytic enzyme, and cells persistently infected with lymphocytic choriomeningitis virus. The lifetimes of excited pyrene and pyrene butyric acid showed only minor changes among normal, transformed, trypsinized or persistently infected cells. However, pyrene, but not pyrene butyric acid, lifetimes were shorter in cell membranes than in homogeneous solvents. The quenching of excited pyrene in cells by quencher molecules was slower than corresponding reactions in homogeneous solutions, indicating that the probe was screened from the quencher by the membrane. Quenching reactions with the pyrene butyric acid probe were similar in cells and homogeneous solvents, which indicated that pyrene and pyrene butyric acid reside in different lipid regions of the membrane. Transformed and trypsinized cells showed increased membrane fluidity, compared with normal and persistently infected cells. Membrane fluidity was determined from the excimer/monomer fluorescence ratios of pyrene and by the polarization of N-pheynl-l-naphthylamine fluorescence. Several techniques distinguished between normal and transformed or trypsinized cells; however, the only parameter unique to RSV transformation was a blue shift of the fluorescence maxima of N-phenyl-l-naphthylamine. This shift, which reflected a less polar environment of N-phenyl-l-naphthylamine in virus-transformed cells, was reversed by trypsinization. Therefore, the shift was apparently due to the presence of a trypsin-sensitive protein unique to the transformed cells. (31 refs)

78-6856 **Characterization of the Avian Sarcoma Virus Protein p60*src*.** (Eng) Brugge, J. S. (Dept. Pathology, Univ. Colorado Medical Center, Denver, CO, 80262); Steinbaugh, P. J.; Erikson, R. L. *Virology* 91(1): 130-140; 1978.

The intracellular distribution of the avian sarcoma virus (ASV) protein p60*src* was investigated in transformed chicken and hamster cells by radioimmunoprecipitation of fractionated cells and by immunofluorescent staining of fixed cells with monospecific antiserum to p60*src*. The *src* protein was found exclusively in the cytoplasmic fraction in both a soluble and an insoluble form. Furthermore, the antigenicity of p60*src* was extremely heat-labile in vitro relative to Pr76, the precursor to the internal structural proteins of ASV. Antibody against p60*src* in serum from rabbits bearing tumors induced by the Schmidt-Ruppin (subgroup D) strain of ASV did not recognize p60*src* from cells transformed by other ASV strains, including Prague C, B77, and Bryan (RAV-50). Reevaluation of the precipitation of p60*src* from NY68-tran formed cells led to the conclusion that there is no reductic in the synthesis or antigenicity of p60*src* when cells are cu tured under conditions nonpermissive for transformation b the mutant virus. (15 refs)

78-6857 **Large-Scale Production, Concentration ar Purification of Rous Sarcoma Virus in Tissu Culture.** (Eng) Dostalova, V. (Inst. Molecular Genetics, Cz choslovak Acad. Sciences, Prague 6, Czechoslovakia); Hloz nek, I.; Mach, O.; Lacinova, J. *Folia Biol (Praha)* 24(4 225-232; 1978.

A method is described for the production of large amoun of purified virus from tissue cultures of chicken cells tran formed by the Prague strain of Rous sarcoma virus, subgrou C. The method is based on the use of roller culture bottle precipitation with polyethylene glycol 6000, and purificatic by zonal centrifugation. Mean yields in cells cultured for 2 wk were 4.9 mg virus/liter of culture medium. (21 refs)

78-6858 **Long-term Karyological Study of RVP_3 T mour Cells Grown In Vitro.** (Eng) Sainerova, I (Inst. Molecular Genetics, Czechoslovak Acad. Science Praha 6, Czechoslovakia); Svoboda, J. *Folia Biol (Prah* 24(4): 242-252; 1978.

The RVP_3 cell line established from an in vivo passaged RV tumor, which originated in a C57BL/6 mouse infected wi the Prague strain of Rous sarcoma virus (RSV), was analyz at different passage levels and characterized virologically ar cytogenetically. The RVP_3 cell line has 2-5 medium-sized large metacentric chromosomes; the majority of the mitos contain about 1 subtelocentric chromosome; and in additio every mitosis contains chromosomal structures correspon ing to the group (termed m-ms) that comprises both minu chromatin bodies and microchromosomes. In three RV monocellular clones with a similar karyotype, the number m-ms increased proportionally to the total number chromosomes in individual metaphases. It was establish that the RVP_3 cell population does not contain any transmis ible agent producing chromosomal changes in mouse cel and that RVP_3 cells are highly malignant. No RSV could rescued from the clone tested. The possibility that m-ms's a generated by chromosome excision followed by replicatic and reintegration is discussed. The accompanying recomb nation events could lead to deletion or loss of proviral s quences adjacent to the region of the chromosome breaks. (1 refs)

78-6859 **Differentiated Expression of Virus Genome Mammalian Cells Transformed by Rous Sa coma Virus.** (Rus) Tatosyan, A. G. (Lab. Leukemia Virolog

r Res. Center, Moscow, USSR); Kiselev, F. L. *Vopr* 24(10): 9-13; 1978.

ly was designed to attempt to verify the hypothesis that specific RNA in rat XC and TWERC cells murine cells, and hamster XPO cells transformed by Rous na virus (RSV), undergoes transcription from different s of integrated viral genome. Incubation of the NA product of RSV with RNA isolated from trans- cells revealed a high level of molecular hybridization 80%) with RNA from cells producing gS-antigen enic XC cells and helper-dependent TWERC cells) red with a low level of hybridization (10%-13%) with irogenic RPV-3 cells. (14 refs)

60 **Demonstration of Marek's Disease Tumor-associated Surface Antigen in Chickens Infected Nononcogenic Marek's Disease Virus and Herpesvirus rkeys.** (Eng) Schat, K. A. (Dept. Avian and Aquatic al Medicine, New York State Coll. Veterinary Medi- thaca, NY, 14853); Calnek, B. W. *J Natl Cancer Inst* 855-857; 1978.

resence of Marek's disease tumor-associated surface an- MATSA) was demonstrated on spleen cells from P-line ns inoculated 5-6 days earlier with herpesvirus of tur- HVT) and SB-1 (a nononcogenic Marek's disease vi- Fluorescence, which was restricted to the cell mem- was more intense on cells from SB-1-infected chickens n those from HVT-infected chickens. Antisera against SA expressed on five Marek's disease lymphoblastoid nes were able to recognize the MATSA present on nfected spleen cells. No viral membrane antigens and a low incidence of viral internal antigens could be strated. (16 refs.)

61 **The Herpesvirus of Marek's Disease and Human Cancer.** (Eng) Makari, J. G. (Makari Res. Englewood, NJ, 07631). *In: Third International Sym- on the Detection and Prevention of Cancer held by the ational Study Group for the Prevention and Detection ncer in New York, April 26-May 1, 1976.* International Group for the Prevention and Detection of Cancer York, NY): Vol. 1(part 1): 1193 pp.; 263-278; 1977.

viously found common antigenicity between glyco- n (gp) antigens from human cancers and those from s of chickens with Marek's disease was explored fur- y a highly sensitive, modified Schutz-Dale technique. rch was made for serum antibodies (ab) to Marek's e herpesvirus (MDHV) in 141 subjects with and with- ncer and for MDHV antigens in the deoxyribose-purine nts (DPF) of normal and cancerous tissues. Serum ab ntigens prepared from MDHV were found in 63% of 65 subjects with nonmalignant diseases, 74% of 69 subjects with carcinoma (ca), and 4/7 subjects with melanoma and sarcoma. Serum ab to gp antigens prepared from herpes simplex virus types 1 and 2 and Epstein-Barr virus were found in only 4% of 52 subjects with nonmalignant diseases, 9% of 54 subjects with ca, and none of the 5 subjects with melanoma and sarcoma. All 8 subjects with early colon and breast ca had serum ab against MDHV, vs 56% of 18 subjects with late disease. MDHV antigens were found in the DPF of all nine cancer types tested, but not in normal lung DPF or in DPF from fibroid uterus. These antigens were not detected with comparable gp antigens extracted from mouse hepatitis virus and influenza virus or with six control tissue antigens prepared from human and chicken tissues. Certain types of cancer were associated with antigens prepared from various strains of MDHV: ie, colon ca was associated with the GA strain, breast, ovary, and lung ca were associated with the CR-64 strain, and liver ca and lymphoma were associated with the GA-2 strain. The associations were found in both the serum ab and DPF studies. This was not the case with the gp antigens from the other herpesviruses investigated. (27 refs)

78-6862 **Murine Mammary Tumor Virus Expression During Mammary Tumorigenesis in BALB/c Mice (Meeting Abstract).** (Eng) Pauley, R. J. (Dept. Cell Biology, Baylor Coll. Medicine, Houston, TX, 77030); Socher, S. H. *J Cell Biol* 79(2, part 2): 358a; 1978. (no refs)

78-6863 **Murine Mammary Tumor Virus (MuMTV) Infection of an Epithelial Cell Line Established from C57BL/6 Mouse Mammary Glands.** (Eng) Vaidya, A. B. (Dept. Microbiology and Immunology, Hahnemann Medical Coll., Philadelphia, PA, 19102); Lasfargues, E. Y.; Sheffield, J. B.; Coutinho, W. G. *Virology* 90(1): 12-22; 1978.

An epithelioid cell line (C57MG) derived from the mammary glands of a 23-wk-old C57BL/6 breeder mouse was found to be susceptible to infection by murine mammary tumor virus (MuMTV). After infection of 10^6 C57MG cells/ml with approx 10^{11} virus particles/ml, there were no changes in all morphological or growth characteristics, but annealing experiments with cellular DNA and complementary MuMTV DNA indicated that the infected C57MG cells had acquired three times as many MuMTV-related DNA sequences as uninfected cells. When high mol-wt cellular DNA was separated from unintegrated relatively low-mol-wt DNA and then hybridized again with complementary MuMTV DNA, the threefold increase was again demonstrated in the high-mol-wt fraction of infected cells vs the noninfected cells. This indicated a high level of MuMTV DNA integration in infected C57MG cells. Infected cells synthesized approx 150 copies of MuMTV RNA per cell, and the concentration was enhanced by the addition of dexamethasone to the culture medium. Uninfected cells had no observable MuMTV RNA

under any conditions. Infected cells released 80 MuMTV virions/cell/24 hr before dexamethasone stimulation and 240 virions/cell/24 hr after simulation. Electron microscopy indicated that the virions were indistinguishable from standard MuMTV. Thermal denaturation profiles were inadequate in determining whether the MuMTV produced by infected C57MG cells was of infecting virus or endogenous C57 virus origin. This in vitro infection of in vivo target cells for MuMTV provides an additional useful research tool. (27 refs)

78-6864 **The Use of Molecular Hybridization to Track the Mode of Transmission and Distribution of Murine Mammary Tumor Viruses. A Model for Etiologic Studies of Human Breast Cancer.** (Eng) Schlom, J. (NCI, NIH, Bethesda, MD, 20014); Colcher, D.; Drohan, W.; Kettmann, R. *Prog Exp Tumor Res* 21: 140-158; 1978.

Molecular hybridization techniques were used to determine whether mouse mammary tumor virus (MMTV) can be introduced into a given mouse via the germ cell line or via a non-germ line mechanism. Labeled 60S-70S RNA from a C3H mouse mammary tumor virus [MMTV(C3H)] was hybridized to an excess of DNA from livers of normal C3H mice, and the unhybridized RNA fraction was isolated. This recycled RNA hybridized to the DNA of C3H mammary tumors, but not to the DNA of C3H livers. Thus, it represents the portion of the MMTV(C3H) genome that is transmitted via a non-germ line mechanism. These sequences were present as provirus in the DNA's of mammary tumors of C3H, RIII, and GR mice, but they were not detected in the DNA's of mammary tumors of C3HfC57BL or BALB/c mice or in the DNA's of normal livers of several mouse strains. Thermal analysis of hybrids also demonstrated qualitative differences in MMTV proviral sequences in different mouse strains. The use of ^{3}H-MMTV complementary DNA indicated quantitative differences in MMTV proviral sequences in different mouse strains and between normal and neoplastic tissues of a given mouse. The complexities of the murine model must therefore be considered in studies dealing with a viral involvement in human breast cancer. (23 refs)

78-6865 **Translation of Mouse Mammary Tumor Virus RNA: Precursor Polypeptides are Phosphorylated during Processing.** (Eng) Nusse, R. (Dept. Virology, Antoni van Leeuwenhoekhuis, Plesmanlaan 122, Amsterdam, Netherlands); Asselbergs, F. A.; Salden, M. H.; Michalides, R. J.; Bloemendal, H. *Virology* 91(1): 106-115; 1978.

The synthesis of viral polypeptides of murine mammary tumor virus (MMTV) was studied by pulse-labeling of MMTV-producing cells and by translating MMTV virion RNA in vitro, in *Xenopus laevis* oocytes. Virus-related polypeptides were detected by immunoprecipitation with monospecific antisera against the major viral proteins gp49 and p24 and analysis of the immunoprecipitates on polyacrylamide gels. In pulse-labeled MMTV-pro ducing cells (Mm5mt/cl), a precursor 73,000-dalto polypeptide was immunoprecipitated by anti-p2 serum (Pr73*gag*). Pr73*gag* comigrated with the 73,00 dalton glycosylated precursor for the envelope pr teins (Pr73*gag*) immunoprecipitated by anti-gp4 serum. Pr73*gag* was, during chase, converted into 76,000-dalton polypeptide that also reacted with the anti-p2 serum (Pr76*gag*). After prolonged incubation, the mature in ternal protein p24 was synthesized. Pulse-labeling with ^{32} and subsequent chasing revealed that phosphate was incor porated into Pr76*gag* but not into Pr73*gag*. Isolated virio 70S RNA of MMTV, microinjected into *Xenopus* oocytes gave rise to the synthesis of Pr73*gag*, Pr763*gag*, and p24, a immunoprecipitated by anti-p24 serum, and the vir core proteins p14 and p10, precipitated by polyvalen anti-MMTV serum. 70S RNA did not instruct synthes of the viral envelope glycoproteins. (27 refs)

78-6866 **Genetic Control of Endogenous Murine Mam mary Tumour Viruses Reinvestigated.** (Eng Bentvelzen, P. (Radiobiological Inst. TNO, 151 Lange Kle weg, Rijswijk, Netherlands); Brinkhof, J.; Haaijman, J. J. *Eu J Cancer* 14(10): 1137-1147; 1978.

Milk samples of progeny mice from crosses between mous strains that differ in the degree of release of endogenous mu rine mammary tumor virus (MuMTV) were tested for th presence of MuMTV antigens by the Sepharose bead im munofluorescence assay. The results indicated that, com pared with nonexpressor BALB/c mouse, a single dominan gene controls the release of MuMTV in C3Hf mouse. Howev er, the low-cancer strain C57BL carries a dominant, epistati gene that can inhibit virus release in hybrids with C3Hf t a large extent. The high-cancer strain GRS harbors a dom nant gene that, in F1 hybrids of all strains tested, causes th release of large quantities of a virus (MuMTV-P) that induce tumors at an early age. Other genetic factors control the re lease of a lesser oncogenic virus in the GRS strain. The ani mals tested for MuMTV antigens were subsequentl force-bred for mammary carcinoma production. Althoug there was a good correlation between virus release at a youn age and tumor development at a late age, a substantial num ber of virus-negative mice developed mammary tumors. (3 refs)

78-6867 **Expression of Mammary Tumor Virus Antige in the Male Secondary Genital Organs of th GRS/A Mouse Strain.** (Eng) Imai, S. (2nd Dept. Pathology Nara Medical Univ., Nara, Japan); Imai, N.; Morimoto, J. Tsubura, Y. *J Nara Med Assoc* 29(3): 503-508; 1978.

Four immunological methods (immunodiffusion, microim munodiffusion, immunofluorescence absorption, and radi oimmunoassay) were compared for their ability to detec mammary tumor virus (MTV) antigen, and a pilot study wa

d out to correlate the expression of MTV antigen in genital organs to the Mtv-2 gene in GRS/A strain mice. immunoassay was the most sensitive method for detect-TV antigen. Studies of tissue extracts of the epididymis he coagulating gland suggested that MTV antigen ssion in these organs might be under the control of the 2 gene locus. (20 refs)

868 **Involvement of Mouse Mammary Tumor Virus in Spontaneous and Hormone-induced Mam- Tumors in Low-Mammary-Tumor Mouse Strains.** Michalides, R. (Div. Virology, Antoni van Leeuwenho-s, Netherlands Cancer Inst., Amsterdam, Netherlands); Deemter, L.; Nusse, R.; Ropcke, G.; Boot, L. *J Virol* : 551-559; 1978.

possible involvement of mouse mammary tumor virus V) in spontaneous and hormone-induced mammary tu- in low-mammary-tumor mouse strains was studied by aring the amounts of MTV DNA and MTV RNA of mary tumors, mammary glands, and other organs of with and without hormonal treatments. Hormone treat- was performed as follows: four hypophyseal isografts implanted, two into each kidney, of C3Hf females at the f 6-8 wk; one hypophysis was implanted into the left y of castrated 020 males at the age of 6-8 wk. Estrone mg/liter) was added to the drinking water throughout hole life-span of the mouse, and 3 mg of progesterone iven sc. The virus-induced mammary tumors contained MTV DNA copies in their cellular genome than the er present in the genome of cells of noninfected tissues. former also contained larger amounts of MTV RNA those found in the lactating mammary glands of these als. Hormone-induced mammary tumors contained the number of MTV DNA copies in their cellular genome d the other tissues of the animals. Hormone treatment ed in an increased expression of MTV RNA in the lac- mammary glands, but this enhanced level of MTV expression was not maintained in the hormone-induced mary tumors. Spontaneous mammary tumors of B/c mice did not contain enhanced amounts of MTV or MTV RNA. (27 refs.)

869 **An Inquiry into the Involvement of Nonhuman Breast Cancer Viruses in the Human Disease: Experiments in Malignant Breast Ductal Stem Cells.** McGrath, C. M. (Dept. Biology, Michigan Cancer dation, Detroit, MI, 48201); Soule, H. D. *In: Mech-ns of Carcinogenesis. Proceedings of the Cold Spring Har-Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring or Laboratory): Origins of Human Cancer. Vol. 4 (Book 99 pp.; 1287-1303; 1977.

ttempt was made to determine if mouse mammary tumor virus (MMTV)- or Mason-Pfizer monkey virus (MPMV)-related information is expressed in malignant breast ductal cells (MCF-7) and is present as a provirus in malignant cell DNA. Line MCF-7 was derived from cells cloned from pleural effusions of a scirrhous carcinoma, which contained cells with prominent histologic and hormonal markers. MMTV-related RNA was detected upon hybridization (hyb) with MMTV complementary DNA (cDNA) in 0.5 M Na+ and under stringent conditions of hyb (hydrolysis with a single-strand-specific nuclease), suggesting extensive sequence homology between MMTV-related RNA in MCF-7 cells and murine breast virus genomic RNA. MMTV-related RNA was not detected in two nonbreast malignant cell lines under identical hyb conditions; ie, MMTV cDNA does not complex nonspecifically with any human cell RNA at the RNA concentrations used. In addition, antigens cross-reactive with MMTV virion antigens were detected in the MCF-7 cells, suggesting that MMTV-related RNA is informational in the malignant breast stem cell. However, MMTV-related DNA sequences were not detected in MCF-7 DNA under hyb conditions capable of detecting one av copy per cell. MPMV-related RNA was not detected in MCF-7 cells using MPMV cDNA representing a minimum of 60% of MPMV RNA, and the major internal protein of MPMV (p27) was not detected by immunofluorescence assay or radioimmunoassay. MPMV sequences were not found in MCF-7 DNA at a significantly higher frequency than that found in normal human cells, which suggests that the normal breast precursor of MCF-7 was not infected by MPMV, at least not in the same manner as that in other human cells. Although the data do not rule out the possibility of information related to MMTV or MPMV in DNA of the human breast carcinoma cells, the inability to detect a major portion of the genome related to either virus in DNA of MCF-7 cells provides a rationale for isolating viruses directly from breast carcinoma cells for use as probes in etiologic studies of breast cancer. (54 refs)

78-6870 **The Relative Hydrophobicity of Oncornaviral Structural Proteins.** (Eng) Marcus, S. L. (Memorial Sloan-Kettering Cancer Center, New York, NY, 10021); Smith, S. W.; Racevskis, J.; Sarkar, N. H. *Virology* 86(2): 398-412; 1978.

The interaction of the major structural polypeptides of murine mammary tumor virus (MuMTV) and Rauscher murine leukemia virus (R-MuLV) with alkyl-agarose derivatives containing hydrocarbon arms of various lengths was examined. Both R-MuLV and MuMTV polypeptides were selectively adsorbed to octylimino (C_8)-agarose and decylimino (C_{10})-agarose columns. The proteins were eluted with buffers containing 8.5 M ethylene glycol. In certain cases, the polypeptides could be removed from the columns only by the addition of detergent to the ethylene glyco-containing buffers. By examining the chromatographic behavior of the polypeptides, and the conditions required for their elution, it was possible to determine the relative potential for the hydro-

phobic interaction (degree of hydrophobicity) of each viral protein. The most hydrophobic MuMTV polypeptide was the glycoprotein gp34, p15(E) and the *gag* precursor prp67 appeared to be the most hydrophobic R-MuLV proteins. The least hydrophobic MuMTV polypeptides were p23 and p16, and those of R-MuLV proteins were the two major internal proteins, p10 and p12. Four degrees of apparent hydrophobicity, from least hydrophobic to strongly hydrophobic, could be discerned by this procedure. The major core proteins (MuMTV p23, R-MuLV p30) of both viruses were slightly hydrophobic, but their major glycoproteins were moderately hydrophobic. The degree of hydrophobicity of oncornaviral polypeptides, as determined by hydrophobic chromatography, to the different subviral components with which the proteins were associated. Hydrophobic chromatography may provide a new parameter for the characterization of oncornaviral polypeptides. (52 refs)

78-6871 **Source and Hormone-Dependence of GIX-gp70 in Mouse Serum.** (Eng) Obata, Y. (Memorial Sloan-Kettering Cancer Center, New York, NY, 10021); Stockert, E.; Yamaguchi, M.; Boyse, E. A. *J Exp Med* 148(3): 793-798; 1978.

Strain 129 mice (not overt producers of virus) were examined to determine the tissue origin and hormone dependence of serum GIX-gp70 (a 70,000 dalton polypeptide distinguished by the type-specific antigen GIX). The source of GIX-gp70 could not be traced to any organ or tissue that is known to be GIX-positive by serological tests. Hematopoietic tissues were excluded as the source of serum GIX-gp70 by tests with reciprocal radiation chimeras made from 129 and 129-GIX- donors and recipients. Thymus and spleen were excluded because excision of these organs did not affect levels of GIX-gp70 in the serum. The serum of young adult 129 males contained approx four times as much GIX-gp70 as adult 129 females and the levels rose with increasing age in both sexes. Castration of 129 males reduced the level of serum GIX-gp70 to that of females, and the level was fully restored by testosterone. Thus, the epididymis and seminal fluid, although rich in GIX-gp70, do not contribute significant amounts of GIX-gp70 to the serum. The level of GIX-gp70 in the serum of testosterone-treated females, although more than double that of untreated females, did not reach the level of normal males, under the conditions tested. This may signify that GIX-gp70 production in males is subject to imprinting by testosterone in early life. Evidently, the main source of GIX-gp70 is a tissue or organ that is common to males and females, is directly or indirectly responsive to testosterone, and has not so far been identified serologically as GIX-positive. (16 refs.)

78-6872 **Xenotropic MuLV are Subject to Restriction by the Fv-1 Locus of the Mouse (Meeting Abstract).** (Eng) Gautsch, J. W. (Dept. Cellular and Developmental Immunology, Res. Inst. Scripps Clinic, La Jolla, CA Jensen, F. C.; Elder, J. H.; Lerner, R. A. *J Cell Biol* 79(part 2): 406a; 1978. (no refs)

78-6873 **Wild Rat Type C Virus: Isolation and Charac terization.** (Eng) Rasheed, S. (Dept. Patholog Univ. Southern California Sch. Medicine, Los Angeles, CA 90033); Charman, H. P.; Gardner, M. B. *Virology* 89(2 605-609; 1978.

C-type virus was isolated from a wild male rat(*Rattus rattu* and compared with the C-type viruses from two strains laboratory rat. The wild rat was injected sc with 200 mg 3-methylcholanthrene, and the resulting fibrosarcoma, whic developed at the inoculation site within 13 mo, was direct cultured. The wild-rat tumor cells were tested for virus pr duction at various passages by the supernatant RNA-depen ent DNA polymerase activity assay. The results of viru purification, neutralization, and interference studies showe that the isolated virus exhibits the general properties of r leukemia virus (RLV) including the RLV-specific p30 ant gen. It showed low infectivity for rat cells and no other sp cies. It was antigenically similar to other RLV strains laboratory rat origin. It is concluded that a C-type viru genome is potentially activable in fetal rats never subjecte to laboratory inbreeding. (12 refs)

78-6874 **Physiochemical, Biological and Serologic Properties of a Leukemogenic Virus Isolat from Cultured RadLV-induced Lymphomas of C57BL/ Mice.** (Eng) Decleve, A. (Cancer Biology Res. Lab., Dep Radiology, Stanford Univ. Sch. Medicine, Stanford, C 94305); Lieberman, M.; Ihle, J. N.; Rosenthal, P. N.; Lun M. L.; Kaplan, H. S. *Virology* 90(1): 23-35; 1978.

A radiation leukemia virus (RadLV/VL_3) produced BL/VL cells, which were derived from a RadLV-induc C57BL/Ka mouse thymic lymphoma, was characterize Physicochemical studies with ^{3}H-uridine-, ^{3}H-thymidin and ^{3}H-leucine-labeled RadLV/V_3, as well as inhibition of t viral reverse transcriptase (RT) by antiserum against M loney murine leukemia virus RT, indicated that the isola was a C-type RNA virus. The virus was not neutralized antibodies prepared against other ecotropic or xenotrop murine C-type viruses, used singly or in combination, but was neutralized by rabbit and mouse anti-RadLV$_3$ seru The inability of RadLV and RadLV/VL_3 to induce cytopat ic changes or transformed cell foci in mink lung cell culture even after addition of xenotropic BL/Ka(X) virus, indicat that the in vitro and in vivo host-age patterns of these virus could not be attributed to the presence of competent or defe tive mink cell focus-forming virus. In co-infection exper ments using live or UV-inactivated viruses, none of t viruses tested was able to interfere with RadLV a RADLV/VL_3. However, purified RadLV/VL_3 protein gp

ficantly interfered with the infectivity of RadLV and LV/VL_3, indicating that the major envelope glycoprotein e C57BL/Ka thymotropic and leukemogenic viruses is ict from other tested viruses. This was supported by the that in competitive radioimmunoassay for $RadLV/VL_3$ that used an anti-$RadLV/VL_3$ antiserum, none of the es competed equivalently to $RadLV/VL_3$ gp71. Other s for the p12 and p30 component of $RadLV/VL_3$ did how this specificity. (20 refs)

875 **The Pattern of Involvement of Murine Lymphoid Tissues by Primary Lymphomas of Dift Cell Lineage.** (Eng) Baird, S. (Veterans Admin. Hosp., La Jolla Village Drive, La Jolla, CA, 92161); Raschke, *lum Pathol* 9(1): 47-50; 1978.

netastatic patterns of several different lymphomas were ared with the recirculation pattern of normal T lymytes. T and non-T lymphomas were induced in newborn B/c mice by injections of Abelson leukemia virus prepais. Many primary T-cell lymphomas migrated in the hoid system in areas occupied by normal recirculating ls (eg, the periarteriolar white sheath of the spleen and hymus). Other lymphomas lacking T-cell markers did how this pattern of migration. This lends support to the ice of classifying human lymphoid neoplasms as either B-derived on the basis of their surface antigen markers morphology in lymph nodes. The data indicate that e lymphomas are good models for studying the metapattern of some human lymphomas under prospective olled conditions. (3 refs)

5876 **Genetic and Immunological Controls of Murine Leukemia Viruses in AKR Mice.** (Eng) Nowin-R. C. (Fred Hutchinson Cancer Res. Center, 1124 Coia St., Seattle, WA, 98104); Baron, J. M. *In: Third Internal Symposium on the Detection and Prevention of cer held by the International Study Group for the Prevenand Detection of Cancer in New York, April 26-May 1,* International Study Group for the Prevention and Deon of Cancer (New York, NY): Vol. 1(part 1): 1193 pp.; 198; 1977.

-leukemic AKR mice, low-leukemic C57L mice, and hybrids were examined for the production of murine emia virus (MuLV) p30 antigen, the production of infecN-ecotropic MuLV (ieMuLV), and the development of unity against various proteins of the endogenous virion. L mice did not produce ieMuLV, and p30 expression in spleens was low. In contrast, AKR mice produced high s of ieMuLV, and p30 expression in the spleens was high. F_1 hybrids produced high titers of ieMuLV and exed high p30 levels in their spleens. Backcross C57L x R x C57L)F_1 mice genetically segregated for the expresof infectious MuLV and p30: 68% produced iMuLV, did not contain detectable virus. This ratio was statistically compatible with a two-gene model for the control of MuLV. Virus-producing backcross mice expressed high levels of p30; most of the nonproducers expressed low p30 levels, but a minor population expressed high p30 levels. The latter represent a phenotype distinct from that of the AKR and C57L parents. AKR and C57L strains produced low titers of natural antibody (ab) against eMuLV; their F_1 hybrids produced anti-MuLV ab in a higher titer than either of the parents. Progeny of the backcross mice that contained iMuLV produced anti-MuLV ab's. Thus, the persistent production of ab against high-titered MuLV in these mice did not result in immunological tolerance toward viral antigens. Mice that did not contain iMuLV could be separated into ab-producing and ab-nonproducing classes. The absence of a detectable ab to MuLV in a mouse was invariably associated with a virus-free phenotype. Overt production of endogenous eMuLV probably served as a major immunogenic stimulus for the production of anti-MuLV ab in these mice. (73 refs)

78-6877 **Acquisition of Oncogenicity by Endogenous Mouse Type C Viruses: Effects of Variations in *env* and *gag* Genes.** (Eng) Devare, S. G. (Lab. Cellular and Molecular Biology, NCI, Bethesda, MD, 20014); Rapp, U. R.; Todaro, G. J.; Stephenson, J. R. *J Virol* 28(2): 457-465; 1978.

Competition immunoassays were used to compare the structural proteins of different groups of highly leukemogenic viruses: dual-tropic isolates derived from the thymuses of preleukemic or leukemic AKR mice and strains generated by in vitro or in vivo passage of a weakly infectious endogenous virus of C3H mouse cells. The results show that three AKR-derived isolates and two C3H passage-derived isolates possess *gag* gene-coded proteins immunologically indistinguishable from those of AKR murine leukemia virus. This observation confirms the results of a previous study in which the major structural proteins of several AKR-derived mink cell focus-inducing isolates were found to be similar to those of AKR-MuLV. In contrast, *gag* gene-coded proteins of two other leukemogenic isolates of C3H origin, including one ecotropic and one dual-tropic virus, were indistinguishable from those of Moloney MuLV. All of the highly leukemogenic viruses, including those of AKR and C3H origin, as well as C3H-derived virus, FC clone 3, possessed common envelope glycoprotein antigenic determinants of a class not exhibited by the nononcogenic ecotropic viruses from which they were derived. The results suggest that oncogenic variants of endogenous ecotropic mouse C-type viruses are derived by genetic recombination. This recombinational event appears to involve the acquisition, by different ecotropic viruses, of a common class of endogenous virus-coded envelope glycoprotein determinants that may be required, but not necessarily sufficient, for leukemogenicity. (19 refs)

78-6878 **A Target Cell Assay for Friend Virus.** (Eng) Steinheider, G. (Albert Einstein Coll. Medicine,

1300 Morris Park Ave., Bronx, NY, 10461); Steeves, R. *Leuk Res* 2(3): 197-200; 1978.

An assay was developed for the in vitro infection and subsequent quantification of the hemopoietic target cells from spleen and bone marrow of DBA/2 mice that can replicate Friend virus (FV). The presence of macroscopic spleen colonies in recipient CDF_1 mice was used to quantify the number of infected FV-releasing cells. DBA/2 mice were bled on two consecutive days and sacrificed. Bone marrow and spleen cells were isolated and cultured with 5×10^4 spleen focus-forming units/ml of FV at 37 C for 1 hr and then injected into CDF_1 mice. After 8 days, the CDF_1 spleens were removed and spleen colonies counted. Inoculation with different dilutions of infected DBA/2 cells revealed a linear relationship between the quantity of infected cells transferred and the number of resulting spleen colonies. Lethal irradiation (5,000 R) of 50% of the infected DBA/2 donor cells before injection yielded 73.8 ± 2.1 colonies from the intact cells but none from the irradiated cells, showing that the production of virus and the generation of spleen colonies requires a living cell and ruling against the passive transfer of cell-adherent virus only. When the numbers of infected spleen and bone marrow cells from bled and unbled DBA/2 donor mice that resulted in spleen colonies in recipient mice were compared, it was concluded that bone marrow had more target cells than spleen and that the hemopoietic stimulus of bleeding was greater in the spleen than in the bone marrow. This assay may prove useful in finding and improving the conditions for true oncogenic transformation by FV in vitro, which was not observed in this experiment. (18 refs)

78-6879 **Antibody-induced Loss of Friend Virus Leukemia Cell Surface Antigens Occurs During Progression of Erythroleukemia In F_1 Mice.** (Eng) Doig, D. (Hamilton, MT, 59840); Chesebro, B. *J Exp Med* 148(5): 1109-1121; 1978.

The ability of anti-Friend leukemia virus (FLV) serum + rabbit complement (C′) to lyse leukemic spleen cells from (B10A x A/WynSn)F_1 and (B10.A x A.BY)F_1 mice was studied. Leukemic cells from 27/28 mice showed high specific lysis (20%-45%) when tested 8-9 days after inoculation of the mice with B-tropic FLV (1,500 focus-forming units iv), but cells of only 5/31 mice had $>20\%$ lysis 30-90 days post-inoculation. Quantitation of FV-induced cell surface antigens (CSA) by absorption of cytotoxic antibodies demonstrated that the antigen levels were 4.5-fold higher in early (8-9 days) leukemic cells than in later cells. No difference in absorption of antibody to H-2d histocompatibility antigens was noted when (C57BL/10 x BALB.B)F_1 anti-(B10.D2 x BALB/c)F_1 (anti-H-2d) serum was absorbed with (B10.A x A/WySn)F_1 early or late or leukemic spleen cells or with normal cells. There were also no changes in H-2K or H-2D antigens. Membrane immunofluorescence studies confirmed the loss of FV-induced CSA in the later stages of leukemia. Acetone-fixed cells showed no difference between early or late F_1 leukemic splee cells when tested for the presence of cytoplasmic antige with conjugated goat anti-Moloney LV. The decrease FV-induced CSA could be reversed after adoptive transf of leukemic cells to lethally irradiated (900 rads) unimm nized congenic hybrid mice, but not after transfer to immu irradiated recipients. When late F_1 leukemic spleen cells we cultured in vitro in the absence of anti-FV antibody, no i crease in FV-induced CSA was noted. Conversely, no d crease in FV-induced CSA occurred in early leukemic splee cells cultured with high concentrations of cytotoxic anti-F serum. The observed decreased antigen expression may repr sent a tumor cell adaptation to host immune pressures gen rated during the course of FV leukemia. (19 refs)

78-6880 **Biosynthesis and Metabolism of Viral Protei Expressed on the Surface of Murine Leukem Virus-infected Cells.** (Eng) Ledbetter, J. A. (Fred Hutchi son Cancer Res. Ctr., 1124 Columbia St., Seattle, W 98104); Nowinski, R. C.; Eisenman, R. N. *Virology* 91(1 116-129; 1978.

Viral proteins expressed on the surface of the Gro virus-induced leukemia E(female)G2 were detected by in mune precipitation assays from detergent lysates of cells th were labeled by the ^{125}I-lactoperoxidase method. These pr teins included gp70 and two glycosylated polyproteins th contained antigens coded by the *gag* gene. The 95,000-dalto polyprotein (gpP95*gag*) reacted with antisera against p3 p12, and p10; the 85,000-dalton polyprotein (gpP85*ga* reacted with antisera against p30 and p12, but not again p10. Neither polyprotein reacted with reverse transcripta antiserum. GpP95*gag* and gpP85*gag* contained glucosami only, but gp70 contained both glucosamine and fucose. Try tic peptide maps of the iodinated polyproteins indicated th gpP95*gag* and gpP85*gag* were highly related. Viral polype tides with the same electrophoretic mobilities as the cell su face gpP95*gag* and gpP85*gag* were also detected by immu precipitation of lysates from cells that were metabolically l beled with radioactive methionine or arginine. In kinetic st dies, gpP95*gag* was labeled rapidly following a 10-min puls in contrast, gpP85*gag* was not detected until late in the cha period, suggesting that this glycosylated polyprotein was processed product of gpP95*gag*. Mapping of arginine-labele tryptic peptides of different *gag* polyproteins supported th assumption. In fact, peptide mapping with isolated viral pr teins demonstrated that gpP95*gag* and gpP85*gag* containe peptides of p30, p15/p12, and p10. The presence of p10 pe tides in both polyproteins was unanticipated, since the gpP8 *gag* did not react in immune precipitation assays with a ti-p10 serum. By peptide mapping, both of the glycosylate polyproteins also appeared highly related to Pr75*gag*, the i tracellular precursor to virion *gag* proteins. The data sugge that gpP85*gag* is a glycosylated cell surface form of the pr mary *gag* precursor Pr75*gag*, and that processing of gpP9 *gag* results in the production of gpP85*gag*. (35 refs)

881 **The Integrated Genome of Murine Leukemia Virus.** (Eng) Steffen, D. (Dept. Biology, Center er Res., Massachusetts Inst. Technology, Cambridge, 02139); Weinberg, R. A. *Cell* 15(3): 1003-1010; 1978.

Southern gel filter transfer technique was used to charac- e the integrated genome of Moloney murine leukemia (M-MuLV) and the genomes of the endogenous mouse es. A study of 10 clones of rat NRK cells independently ted by M-MuLV indicated a minimun of 15 integration into which the M-MuLV provirus could be inserted. No mon integration site was observed among these clones. es productively infected by M-MuLV acquired multiple iruses, but infected cells unable to produce virus con- d only one M-MuLV provirus. Once established, the in- ted genomes were stable for at least two years after ini- infection. A spectrum of *Eco*RI-cleaved mouse DNA nents containing endogenous MuLV genomes was de- d through the use of M-MuLV probes. DNA's of differ- nbred laboratory mouse strains yielded similar provirus erns, with each strain showing minor characteristic dif- ces. In some instances, mouse cells infected by M-MuLV aled additional proviruses beyond those seen in uninfect- ells. DNA's from three different M-MuLV-induced nomas indicated, as in rat cells, multiple possible integra- sites. (20 refs)

882 **T1 Oligonucleotide Maps of Moloney and HIX Murine Leukemia Viruses.** (Eng) Faller, D. V. logy Dept. and Center for Cancer Res., Massachusetts Technology, Cambridge, MA, 02139); Hopkins, N. *logy* 90(2): 265-273; 1978.

genomes of a HIX virus, its putative ecotropic parent loney IC), and another clonal isolate of Moloney virus loney clone-1) were studied by RNase T1 oligonucleotide ysis. HIX and Moloney IC shared 42 out of 51-53 of their yzable T1 oligonucleotides, and the two clonal isolates loloney virus shared 46 T1 oligonucleotides. Each virus possessed some oligonucleotides not found in the others. d on oligonucleotide mapping, it was concluded that: nucleotides shared by HIX and Moloney viruses proba- ie in the same relative positions on their genomes; the nucleotides found in Moloney IC but not HIX, and vice a, are clustered in corresponding regions in the 3′ halves ie Moloney IC and HIX maps; and the oligonucleotides differ between the two clonal isolates of Moloney virus cattered along the 5′ half of the Moloney IC oligonucleo- map. (26 refs)

883 **Host Response Against Oncorna Virus Induced Lymphomas in Mice.** (Eng) Becker, S. (Dept. nor Biology, Karolinska Inst., S-104 01 Stockholm 60, den); Klein, E. *In: Advances in Comparative Leukemia earch 1977. Proceedings of the VIIIth International Symposium on Comparative Research on Leukemia and Related Diseases, held in Amsterdam, The Netherlands on 22-26 August, 1977.* Bentvelzen, P.; Hilgers, J.; Yohn, D. S., eds. (New York: Elsevier/North Holland Biomedical Press): 503 pp.; 61-68; 1978.

The host response against oncornavirus-induced lymphomas in mice was first demonstrated by transplantation immunity and then by the presence of antibodies reacting with the cell surface. With the development of in vitro methods and the discovery of various lymphocyte subpopulations, attention was focused on cell-mediated killing effects. Three cell types with killing potential can be distinguished: lymphocytes mediating antibody-dependent killing, sensitized T cells, and natural killer (NK) cells. The reactivity to cell-mediated cytotoxicity in vitro do not, however, correlate. Two serologically cross-reacting lymphoma culture lines (YAC-1 and RBL-5) differ in their sensitivity to cell-mediated cytotoxicity by both NK and sensitized T cells. A cell line selected from YAC for low amounts of Moloney cell-surface antigen recognized by mouse antibodies (YAC-IR) does not show decreased sensitivity to the killing effect of either NK or sensitized T cells. Histocompatibility restriction prevails in short-term cytotoxic tests with sensitized effectors. In cold target inhibition tests with A x C57BL F_1 (H-2a, H-2b), but not C57BL (H-2b), effectors, anti-RBL-5 (H-2b) cytotoxicity was inhibited by YAC-1 (H-2a), indicating the recognition of both H-2a and H-2b target cells. When F_1 effector spleen cells were cultured in vitro in the presence of RBL-5 cells, effector cells against RBL-5 were selected with regard to histocompatibility restriction, as indicated by the fact that YAC-1 cells were not inhibitory. (27 refs)

78-6884 **Biological, Immunological, and Biochemical Evidence that HIX Virus is a Recombinant Between Moloney Leukemia Virus and a Murine Xenotropic C Type Virus.** (Eng) Fischinger, P. J. (Lab. Viral Carcinogenesis, NCI, Bethesda, MD, 20014); Frankel, A. E.; Elder, J. H.; Lerner, R. A.; Ihle, J. N.; Bolognesi, D. P. *Virology* 90(2): 241-254; 1978.

Various characteristics of HIX virus were studied to determine its origin and relationship to other murine C-type oncornaviruses. Cloned amphotropic HIX virus adapted to grow in human RD cells (HIX-RD) could enter mouse cells but essentially lost the capacity to propagate in them. The neutralizing antibody-accessible determinants on HIX and HIX-RD resembled those of Moloney murine leukemia virus (M-MuLV) and, to a lesser extent, those of Friend or Rauscher MuLV and two murine xenotropic viruses (MuX). The entire *gag* region structural proteins of HIX appeared to be very similar or identical to those of M-MuLV. HIX and HIX-RD gp70 polypeptides were not mixtures of MuX and M-MuLV gp70's but exhibited type-specific determinants different from known MuLV's. Tryptic peptide maps of the gp70's of HIX-type viruses indicated that HIX virus is the product of recombination between ecotropic and xenotropic

viruses within the envelope gene. There appeared to be little if any HIX-specific complementary DNA sequences that were not a part of or closely related to M-MuLV RNA. (46 refs)

78-6885 **Mammalian Retrovirus-associated RNase H Is Virus Coded.** (Eng) Lai, M. T. (Tumor Virology Lab., Salk Inst., San Diego, CA, 92112); Verma, I. M.; Tronick, S. R.; Aaronson, S. A. *J Virol* 27(3): 823-825; 1978.

The virus-coded nature of the RNase H activity of a temperature-sensitive Rauscher murine leukemia virus (R-MuLV) mutant with thermolabile polymerase activity (*ts*29) was studied. Both the DNA polymerase and RNase H activities of the mutant viral enzyme were two to three times more thermolabile than the corresponding activities from the wild-type R-MuLV. A wild-type (phenotypic) revertant of *ts* 29 was isolated in which the kinetics of heat inactivation of the DNA polymerase and RNase H were comparable to that of the wild-type viral reverse transcriptase. The restriction to infection by two other R-MuLV mutants (*ts*17 and *ts*19, which are also defective in early postpenetration functions) did not appear to be associated with a measurable function of the viral enzyme. The thermolability of the RNase H associated with *ts*29 reverse transcriptase demonstrates that this activity, as well as that of the DNA polymerase, is a product of the mammalian C-type viral genome. The two activities appear to be localized on the same polypeptide chain. (18 refs.)

78-6886 **Characteristics of Cellular RNA in Viral Leukemia.** (Rus) Butenko, Z. A. (Inst. Problem Oncology, Kiev, USSR); Smirnova, I. A. *Vopr Onkol* 24(10): 18-23; 1978.

This study was designed as an attempt to evaluate characteristic features of polyadenylate rich (poly-A) sequences in RNA from Rauscher leukemia virus (RLV)-transformed cells. RNA specimens were isolated from the spleens of BALB/c mice inoculated with RLV and of leukemia-free BALB/c mice. There was no difference in content of cytoplasmic poly-A rich RNA between the leukemic and normal cells, while the content of nuclear poly-A rich RNA in leukemic cells was slightly greater than that in normal cells. Electrophoretic analysis of nuclear poly-A rich RNA showed the presence of additional 30-35 S fraction in leukemic cells, which was absent in normal cells. (29 refs)

78-6887 **Biosynthesis of Rauscher Leukemia Viral Proteins.** (Eng) Arlinghaus, R. B. (Biology Dept., Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030); Jamjoom, G. A.; Arcement, L. J.; Naso, R. B.; Karshin, W. L. *In: Third International Symposium on the Detection and Prevention of Cancer held by the International Study Group for the Prevention and Detection of Cancer in New York, April 26-May 1, 1976.* International Study Group for the Prevention and Detection of Cancer (New York, NY): Vol. 1(part 1): 1193 pp.; 293-309; 1977.

The synthesis of murine leukemia viral proteins was investigated by immune precipitation of ^{35}S-methionine pulse-labeled and chased cultures of Rauscher murine leukemia virus (RLV)-infected JLS-V16 cells. The RLV structural proteins were found to be synthesized in infected cells by way of high-mol-wt precursor polyproteins. In a working model for the biosynthesis of RLV proteins, Pr1a+b, Pr2a+b, and Pr3 [approx 200,000 daltons (200K), 90K, and 80K, respectively] are primary gene products derived by translation of 35S viral RNA. Pr3 arises by a translational control mechanism in which ribosomes detach from the 35S viral messenger RNA after translating Pr3. However, the ribosomes can proceed to translate the polymerase gene in 1/10-20 times to yield Pr1a+b. Pr1a+b thus is cleaved to form reverse transcriptase (RT)-specific proteins [Pr RT1 (145K), 2 (135K), and 3 (85K)] and, possibly, Pr3. Viral proteins p30, p15, p12, and p10 and RT are contained in Pr1a+b, gp69/71 and p12E are contained in Pr2a+b. Pr1b may be derived from Pr1a by proteolytic cleavage or some other posttranslational alteration. Pr2a and Pr2b are assumed to have the same core polypeptide that is glycosylated to different extents during or after translation to produce Pr2a or Pr2b. p30, p15, p12, and p10 are mainly generated by a series of cleavages of Pr3, producing Pr4, Pr5, and Pr6 (65K, 55K, and 45K) in that order. p10 is produced by cleavage of Pr4 to Pr5, p15 by cleavage of Pr5 to Pr6, and p30 and p12 by cleavage of Pr6. Treatment of infected cells with a proteolytic enzyme inhibitor such as tolylsulfonylphenylalanyl chloromethyl ketone caused a build-up of Pr1a+b and prevented the formation of mature structural proteins and RT. The main feature of this model is that a translational control mechanism exists that results in synthesis of a much lower amount of RT than viral structural proteins. (33 refs)

78-6888 **Inhibition by RNA of RNase H Activity Associated with Reverse Transcriptase in Rauscher Murine Leukemia Virus Cores.** (Eng) Sarngadharan, M. G. (Dept. Cell Biology, Litton Bionetics, Inc., Bethesda, MD, 20014); Kalyanaraman, V. S.; Gallo, R. C. *J Virol* 27(3): 568-575; 1978.

Virion cores of Rauscher murine leukemia virus (R-MuLV) were examined to determine if the absence of detectable RNase H activity in these fractions was a result of some selective inhibition. Earlier findings that R-MuLV cores, when isolated by a density gradient, show no detectable RNase H activity were confirmed. The absence of RNase H activity in the core fractions was shown to be due to a selective inhibition of this activity by viral RNA. Direct evidence that viral RNA-mediated inhibition of the RNase H activity was the

cause of the apparent absence of RNase H activity in the isolated core fraction was obtained by studying the effect of viral and other RNAs on RNase H purified from isolated viral cores. Irrespective of the substrate used for measurement, the enzyme was generally inhibited by a variety of natural and synthetic RNAs. Although viral RNA was a strong inhibitor, polyguanylic acid was by far the most potent inhibitor of the reverse transcriptase-associated RNase H. The RNase H activity associated with a highly purified preparation of simian sarcoma virus reverse transcriptase was also similarly inhibited by RNA, suggesting that this property may be general for mammalian RNA tumor viruses. A rabbit anti-reverse transcriptase IgG inhibited both the reverse transcriptase and RNase H activities of the enzyme purified from cores. Overall, the results are consistent with the idea that RNase H and reverse transcriptase are two activities present on the same protein molecule. (21 refs.)

78-6889 **A Study of the Synthesis and Processing of Rauscher Leukemia Virus-specific Polypeptides in Infected Cells and Their Assembly into Virus Particles.** (Eng) Jamjoom, G. A. (Univ. Texas Health Science Center, Houston Graduate Sch. Biomedical Sciences, Houston, TX). *Diss Abstr Int [B]* 39(2): 666; 1978. (no refs)

78-6890 **Physical Association of Murine Leukemia Virus Envelope Glycoprotein and Mouse Major Histocompatibility Antigens on Leukemia Cell Surfaces and Their Recognition as Target Antigens by Cytotoxic T-Lymphocytes (Meeting Abstract).** (Eng) Zarling, D. A. (Univ. Wisconsin, Madison, WI, 53706); Watson, A.; Duke, R. E.; Keshet, I.; Bach, F. H. *J Cell Biol* 79(2, part 2): 401a; 1978. (no refs)

78-6891 **Persistence of Sindbis Virus in Oncornavirus-producing Cultures.** (Rus) Pogodina, V. V. (Inst. Poliomyelitis and Viral Encephalitis, Moscow, USSR); Fokina, G. I.; Kiseleva, L. L.; Graevskaia, N. A.; Sito, A. F.; Ivanov, A. P. *Vopr Virusol* (2): 196-201; 1978.

Two continuous cell lines (PKR-1 and PKR-2) were derived from a primary culture of BALB/c embryo cells infected with Rauscher leukemia virus (RLV). PKR-1 and PKR-2 were infected with Sindbis virus (SV) and/or repeatedly infected with RLV. The cultures, maintained for 18 mo, retained their ability to produce C-type oncornavirus. Marked reverse transcriptase activity was detected in line PKR-1 from passages 19 to 68 and in PKR-2 from passages 26 to 70. The lines contained the murine oncornavirus-specific antigen gs-1. Characteristic features of SV persistence were development of homologous interference with SV without interferon participation and progressive repression of arbor virus and oncornavirus function. (8 refs)

78-6892 **B-MuX: A Unique Murine C-type Virus Containing the "*env*" Gene of Xenotropic Viruses and the "*gag*" Gene of the Ecotropic Virus.** (Eng) Ihle, J. N. (Cancer Biology Program, NCI Frederick Cancer Res. Center, Frederick, MD, 21501); Fischinger, P.; Bolognesi, D.; Elder, J.; Gautsch, J. W. *Virology* 90(2): 255-264; 1978.

A unique xenotropiclike virus (B-MuX) isolated by clonal purification from iododeoxyuridine-induced Kirsten sarcoma virus-transformed BALB/c nonproducer cells was characterized. B-MuX had the host-range properties of other murine C-type xenotropic viruses. It reciprocally shared interference properties with BALB:virus-2 (BALB-1), and the neutralization spectra suggested that the two viruses had very similar, if not identical, neutralizing antibody-eliciting determinants on their gp70 polypeptides. B-MuX contained an *env* gene similar to that of the endogenous BALB-2 xenotropic virus and *gag* gene products similar to those of the endogenous ecotropic virus. The p30 of B-MuX was structurally similar to that of the endogenous ecotropic virus and differed from the p30 of the BALB/c xenotropic virus, as determined by tryptic peptide analysis. The results suggest that B-MuX is a new type of endogenous xenotropic virus or a recombinant between the endogenous xenotropic and ecotropic viruses. The *gag* gene region does not contribute to this virological property. (34 refs)

78-6893 **Surface Morphology of Normal and Virus-transformed Cells In Vitro.** (Rus) Samil'chuk, E. I. (Lab. Experimental Oncology, Inst. Experimental Pathology and Therapy, Acad. Medical Sciences, USSR, Sukhumi, USSR); Timanovskaia, V. V.; Kukava, G. G. *Tsitologiia* 20(10): 1205-1208; 1978.

The morphology of the mink lung cell line Mv1Lu and its Kirsten sarcoma virus-transformed counterpart, Ki-Mv1Lu, was studied in vitro. In monolayer culture, the morphology of the normal cells differed sharply from that of the transformed cells. The Mv1Lu monolayer consisted of uniform, flat, polygonal cells with surface microvilli. At low cell density, foci of dense growth consisting of cells morphologically identical to those of the monolayer were seen. The transformed cells were characterized by morphological heterogeneity; the cells were polygonal, flat, spherical, and spindle-shaped. Microvilli, blebs, and filopodia were seen on the surface. The morphology of the Ki-Mv1Lu cells was independent of cell density. There was, however, nothing in the cell-surface morphology that was absolutely specific for the transformed cells. (10 refs)

78-6894 **Comparison of the Genomic Organization of Kirsten and Harvey Sarcoma Viruses.** (Eng) Shih, T. Y. (Lab. Tumor Virus Genetics, NCI, Bethesda, MD, 20014); Williams, D. R.; Weeks, M. O.; Maryak, J. M.; Vass, W. C.; Scolnick, E. M. *J Virol* 27(1): 45-55; 1978.

The genomic RNA's of Kirsten murine sarcoma virus (Ki-MuSV), Harvey murine sarcoma virus (Ha-MuSV), and the replication-defective endogenous rat virus were compared, and their structure and function were correlated. Genome organization and sequence homology were studied by fingerprinting large RNase T1-resistant oligonucleotides (ON) and by cross-protecting homologous ON against RNase A and T1 digestion with complementary DNA (cDNA) prepared from each of the other viral RNA's. Ki-MuSV and Ha-MuSV RNA shared a series of rat-derived ON beginning approx 1 kilobase (kb) from the 3′ end and extending to within 1.5 kb at the 5′ end of Ki-MuSV RNA. The total map distance covered was about 5.5 kb. The eight ON covering the 1.5 kb assigned to the 5′ end of Ki-MuSV RNA were not found in Ha-MuSV RNA. However, by protection of Ki-MuSV RNA with cDNA from the rat virus, 5/8 ON could be designated as rat genetic information. Since Ha-MuSV is approx 6.5 kb and Ki-MuSV is 8.0 kb in size, the major difference between them is the 1.5 kb at the 5′ end of Ki-MuSV RNA not present in Ha-MuSV RNA. When the viral RNA's were translated in vitro in cell-free systems, Ki-MuSV yielded a major product of 50,000 daltons, Ha-MuSV RNA a major product of 22,000 daltons. These polypeptides are clearly distinguishable from each other upon tryptic mapping and apparently are translated from the full-genome-length viral RNA, suggesting that they are products of the 5′ portions of the viral RNA. They may provide the necessary protein markers for identifying in vivo virus-coded proteins. (23 refs)

78-6895 **In Vitro Isolation of Stable Rat Sarcoma Viruses.** (Eng) Rasheed, S. (Dept. Pathology, Univ. Southern California Sch. Medicine, Los Angeles, CA, 90023); Gardner, M. B.; Huebner, R. J. *Proc Natl Acad Sci USA* 75(6): 2972-2976; 1978.

At low passage, a Sprague-Dawley (SD-1) rat embryo culture released an endogenous ecotropic C-type leukemia virus (SD-RaLV) and, after about 20 further passages, it underwent spontaneous transformation. The SD-RaLV released from the transformed cells did not cause rapid transformation of other rat embryo cells. However, when the transformed cells were cocultivated repeatedly with three different chemically transformed and serially transplanted rat tumor cell lines (4-nitroquinoline oxide-induced sarcoma, dimethylhydrazine-induced carcinoma, and N,N′-2,7-fluorenylene bis-2,2,2-trifluoroacetamide-induced hepatoma), rapidly fibroblast-transforming "sarcoma" viruses (RaSV) were recovered after each attempt. RaSV was not recovered from one of these tumor cell lines before transplantation, and focus-forming virus could not be rescued from these same tumor cells C-type by cocultivation with other cells releasing heterologous C-type viruses. Foci were induced on normal rat kidney (NRK) and several other rat embryo cell strains within 7-15 days, and both productive and nonproductive NRK clones were derived. The productive clones were positive for rat-specific p30 antigen and the RaSVs released were serially transmitted to other rat embryo cells. RaSV genom was rescued from the nonproductive clones by superinfectio with SD-RaLV, wild rat C-type virus, and several heterol gous C-type viruses. It is concluded that naturally occurri transformation-specific (*src*) genes are being recovered in v tro in the form of stable sarcoma viruses from cells into whi no sarcoma virus had apparently been introduced. The viruses differ from the Kirsten and Harvey strains of muri sarcoma virus in that they apparently contain no murine le kemia virus sequences and are of purely rat origin. (41 ref

78-6896 **Characterisation of a Tumor-Specific Antig on the Surface of Feline Lymphosarcoma Cell** (Eng) Snyder, H. W. (Lab. Viral Oncology and Veterina Oncology, Memorial Sloan-Kettering Cancer Center, Ne York, NY, 10021); Hardy, W. D.; Zuckerman, E. E.; Fleiss er, E. *Nature* 275(5681): 656-658; 1978.

A 70,000-mol-wt protein that exhibited antigenic determ nants in common with the feline oncornavirus-associated c membrane antigen (FOCMA) was identified on the surfa of feline lymphosarcoma (LSA) cells and cultured tran formed feline lymphoblastoid cells. Cell surface molecul carrying FOCMA determinants were characterized by e zymatic radioiodination of viable cells, precipitation with ty ing serum from detergent lysates, and analysis of protei in immunoprecipitates by sodium dodecyl sulfate-polyacryl mide gel electrophoresis (SDS-PAGE). In LSA cells, vir antibodies in FOCMA typing serum always precipitated single protein species, regardless of whether the cell showe concomitant expression of feline leukemia virus (FeL structural antigens. In contrast, immunoprecipitation FeLV gp70 molecules with FeLV-neutralizing serum was r stricted to FeLV-positive cells. Absorption experimen proved that the 70,000-mol-wt FOCMA molecule in LS cells was seriologically distinguishable from surface antige related to FeLV structural proteins. FOCMA-carryin FeSV-transformed nonproducer mink cells gave two protei species approx 85,000 and 65,000 mol-wt upon SDS-PAG after precipitation by FOCMA antiserum. (18 refs)

78-6897 **The Retrovirus Particles in Human Myelom Cells RPMI8226: Morphological, Biochemica Immunological and Infective Transmission Studies.** (En Grofova, M. (Cancer Res. Inst., Slovak Acad. Sciences, 88 32 Bratislava, Czechoslovakia); Popovic, M.; Ogura, H Matoska, J.; Lizonova, A.; Nilsson, K.; Kuzela, S. *Neoplasm* 25(4): 423-437; 1978.

The morphological, biochemical, and immunological prope ties of a retrovirus (RPMI8226V) isolated from RPMI822 human myeloma cells were investigated, and propagation the virus in various animal and human cells was studie Ultrastructural observations revealed that RPMI8226V pa ticles have a C-type morphology. They were classified int

ree categories: immature and mature particles indistinishable from typical C-type mammalian oncornaviruses d typical C-type particles with an intermediate membrane. ıdding particles in secondarily infected human neoplastic lls contained doughnut-shaped nucleoids characteristic of type particles. ^{3}H-uridine-labled RPMI8226V particles had ouoyant density of 1.17 g/ml in a sucrose gradient containg high mol wt RNA, and the distribution of viral structural oteins upon sodium dodecyl sulfate-polyacrylamide gel ectrophoresis was characteristic of that of oncornaviruses. ıe mol wt of the internal structural proteins ranged from ,000 to 30,000 daltons. The virus contained an Mg-dependt reverse transcriptase (RT). The cellular homogenate and ral concentrate from RPMI8226 cultures did not react with ıtibodies against murine leukemia virus, feline leukemia rus, RD114, Mason-Pfizer monkey virus, simian sarcoma ukemia virus, and avian leukemia/sarcoma virus. The only action occurred with anti-bovine leukemia virus (BLV) anodies. However, anti-BLV serum inhibiting the RT activity BLV to 60% did not cross-react with the RT of PMI8226V. In contrast to BLV concentrates, neither XC or KC cells showed syncytia formation by RPMI8226V. PMI8226V replication was restricted to human tumor and ormal human glialike cells. The data indicate that PMI8226V may be of bovine origin. (40 refs)

8-6898 **Induction of Deoxythymidine Kinase Activity in Several Mammalian Cell Lines after Infection ith Six Different Strains of Equine Herpesvirus Type 1 EHV-1).** (Eng) Allen, G. P. (Dept. Microbiology, Univ. Mississippi Medical Center, Jackson, MS, 39216); McGowan, J. ; Bryans, J. T.; Randall, C. C.; Gentry, G. A. *Virology* 90(2): 51-359; 1978.

he ability of six strains of equine herpesvirus type 1 (EHV-1) induce deoxythymidine kinase (dTK) activities in mouse T3 cells, horse embryo fibroblasts (KyED), equine transional cell carcinoma cells (HT), and owl monkey kidney cells OMK) was studied. Increased deoxythymidine triphosphate TTP)-resistant dTK activity was observed after infection f all cell types with any of the six strains of EHV-1. Increased levels of dTTP-resistant dTK were also detected in ver homogenates derived from Syrian hamsters infected ith EHV-1. This activity appeared to be virus-coded. HV-1 appeared to induce a dTK activity in HT and KyED ells that comigrated in polyacrylamide gels with the cytosol inase of the host cell. Replication of wild-type EHV-1 in 3T3 ells was inhibited by arabinosylthymine (ara-T), but replicaon of the virus in OMK, HT, and KyED cells was considerbly more resistant to inhibition by ara-T. The data indicate hat infection of cells with any strain of EVH-1 results in the nduction of a new, virus-coded dTK activity. (40 refs)

78-6899 **Transformation of Warts to Malignancy in Alimentary Carcinoma in Cattle.** (Eng) Jarrett, W. F. (Dept. Veterinary Pathology, Univ. Glasgow, Bearsden Road, Glasgow G61 1QH, Scotland). *Bull Cancer (Paris)* 65(2): 191-194; 1978.

The naturally occurring high incidence of alimentary carcinoma in beef cattle in the highland areas of Britain offers an excellent opportunity to study the interactions between a papilloma virus and an environmental chemical, possibly derived from bracken fern, that has putative mutagenic and immunosuppressive properties. This development of carcinoma is associated with the presence of bracken fern on high-incidence farms, and many of the carcinomas arise in preexisting virus-induced papillomas. Papillomas are much commoner and occur in greater numbers in animals of all ages on the cancer farms than in cattle on lowland farms. Carcinomas have only been seen in cattle >6 yr old. The virus has been isolated, visualized, and purified; it produces papillomas when inoculated into the alimentary tract and skin. A total of 165 carcinomas were found in 80 cows with squamous carcinoma of the alimentary tract. They were distributed as follows: palate 4%, pharynx 8%, tongue 7%, esophagus and groove 41%, and rumen 30%. Papillomas or warts of the squamous epithelium lining the upper alimentary tract were found in 96% of these cows. There was a range of tumors from benign papillomas to papillomas with areas of malignant transformation to frank ulcerating and invasive carcinoma. (5 refs)

78-6900 **Some Physical Properties of a Human Laryngeal Papillomavirus.** (Ger) Liebermann, H. (Friedrich-Loeffler-Institut fur Tierseuchenforschung, DDR-2201 Insel Riems, uber Greifswald, E. Germany); Solisch, P.; Hahnefeld, H. *Arch Geschwulstforsch* 48(6): 552-558; 1978.

Ultracentrifugation of a human laryngeal papillomavirus produced particles sedimenting at 130S and 214S. Electron microscopy revealed the presence of 37-nanometer (nm) and 49-nm particles, with the latter having a buoyant density in CsCl gradients of 1.34 g/ml. This virus resembles a polyoma virus. (19 refs)

78-6901 **In Vitro Transcription of Polyoma DNA.** (Eng) Monjardino, J. (Div. Cell Studies, Royal Free Hosp. Sch. Medicine, 8 Hunter St., London WC1N 1BP, England); James, A. *Biochem Biophys Res Commun* 84(3): 618-626; 1978.

In vitro transcription of supercoiled DNA from nondefective polyoma virus (PV) by *Escherichia coli* RNA polymerase was successfully carried out, and the resulting complementary RNA (cRNA) was seen to be double stranded to a large extent, longer than the coding strand, and initiated from a limited number of sites. The incubation mixture for RNA synthesis contained 20 μg/ml PV DNA I, 75 μg/ml *E. coli*

RNA polymerase, and nucleotides including ^{3}H-GTP (0.15 Ci/millimole). Results of chromatographic separation of the double-stranded RNA product on CF11 cellulose and pancreatic RNA digestion, followed by cRNA annealing, proved that the transcription was at least partially symmetric. Electron microscope visualization of the transcription complexes showed long RNA chains up to 3x the length of the template strand. In the presence of rifampicin, transcription was usually initiated from 2-3 initiation sites, proceeding at a rate of 16 nucleotides/sec under suboptimal conditions. When 32 transcription complexes were lined up on linear DNA molecules, it was evident that the RNA could not have originated from a common initiation site. Further, cRNA chains in some complexes differed in length by more than a transcript of the entire DNA template. These findings support the hypothesis that transcription took place from both DNA strands. (16 refs)

78-6902 **Expression of Polyoma Virus In Heterokaryons Between Embryonal Carcinoma Cells and Differentiated Cells.** (Eng) Boccara, M. (Departement de Biologie Moleculaire, Institut Pasteur, 25 rue du Dr. Roux, 75015 Paris, France); Kelly, F. *Virology* 90(1): 147-150; 1978.

Polyoma virus (PV)-resistant PCC3/A/1 embryonal carcinoma cells were fused with two types of susceptible cells: differentiated teratoma-derived PCD3 cells, which are fully permissive for PV, and BHK21 cells, which can express only the early viral genes. Cells from one parent were infected with 20 plaque forming units of PV, fused 4 hr later with the other ^{3}H-thymidine labeled parent using β-propiolactone-inactivated Sendai virus, and examined by autoradiography 48 hr post-infection for the presence of V antigen or radioactively labeled nuclei. When infected PCC3/A/1 cells were fused with PCD3 cells, 20% of the heterokaryons were V antigen-positive. Both parent cells were necessary for viral expression, suggesting that the virus entered the PCC3/A/1 cells but was expressed only upon fusion with permissive cells. Fusion of infected PCD3 cells with PCC3/A/1 cells resulted in 60% antigen-positive heterokaryons, a percentage comparable to that of infected PCD3 homokaryons or isolated PCD3 cells. Nonpermissive preinfected BHK21 cells produced 5% antigen-positive heterokaryons when fused with PCC3/A/1 cells, compared with no apparent staining in unfused, infected BHK21 cells or BHK21 homokaryons. These experiments indicate that blocked response to PV in pluripotent teratocarcinoma cells occurs after penetration of the viral particle but before the synthesis of the T antigen, and that susceptibility to infection in the differentiated cells is dominant over resistance in the embryonal carcinoma cells. (10 refs)

78-6903 **Isolation of Polyoma Viruses Lacking Endonuclease *Hin*dIII Sites.** (Eng) Anderson, D. M. (Roche Inst. Molecular Biology, Nutley, NJ, 07110); Bendig, M. M.; Folk, W. R. *Virology* 89(2): 637-642; 1978.

Spontaneous mutants of polyoma virus that have specific a terations at one of two endonuclease *Hin*dIII sites in th polyoma genome (one in the early region, the other in th late region) were isolated and partially characterized. Th viruses were divided into two groups on the basis of the genome structure and complementation requirements: Grou I viruses did not require complementing genomes in order t form plaques, but Group II viruses did. Infection by grou I viruses produced homogeneous populations of DNA, bu infection by Group II viruses always produced two DN species, regardless of the number of attempts to plaque-puri them. In almost every instance, a DNA without one *Hin*dI site was accompanied by a DNA having an alteration at th other *Hin*dIII site. Many of the viruses in both groups synth sized viral DNA at 32 and 39 C, although several Group mutants did not synthesize form I DNA as well at 39 C a at 32 C, indicating thermolability of early gene products. Se eral of these mutants will be useful in probing the functio of the polyoma genome. Group I mutants may express altere early functions. In addition, most of these viruses are capab of proceeding through a normal lytic infection and ma therefore, be more useful as cloning vehicles than wild-typ polyoma DNA. Group II mutants, altered in the early or la region, are difficult to grow in large amounts, and the in dividual species of the pairs of mutants must be separate before the extent and effects of the alterations can be define (28 refs)

78-6904 **Polyoma Virus High Molecular Weight Nuclea RNA Codes for Capsid Protein VP2 In Vitr** (Eng) Kamen, R. I. (Transcription Lab., Imperial Canc Res. Fund, London WC2A 3PX, England); Wheeler, T Smith, A. E. *Virology* 89(2): 461-474; 1978.

An attempt was made to determine whether polyoma viru (Py) nuclear RNA molecules, which contain messenge RNA-like sequences but which are assumed not yet exter sively spliced, can direct the synthesis of viral proteins i vitro. RNA extracted from the nuclei of 3T6 mouse cells lat after infection by Py was translated in vitro to give on predominant polypeptide. This polypeptide was identified a virion protein VP2 by polyacrylamide gel electrophoresi specific immunoprecipitation, and tryptic peptide analysis The active nuclear RNA species sedimented between 15S an 50S on sucrose gradients after denaturation. The bulk of th active viral nuclear RNA did not bind to oligo(dT)-cellulos and synthesis of Py VP2 was inhibited by m^{7}Gp under cond tions in which translation of Py-complimentery RNA an EMC RNA are not inhibited. It is concluded that VP2 codin activity is not only a function of mature cytoplasmic 19 RNA, but also of Py nuclear RNA, which is probably cappe but not polyadenylated. Determination of the size of the ac tive RNA molecules indicated that all size classes of nuclea RNA have VP2 coding activity and that this activity is un likely to result from contamination of the high mol wt RNA with aggregated 19S RNA. (49 refs)

-6905 **Evaluation of Normal and Neoplastic Human Tissue for BK Virus.** (Eng) Israel, M. A. (Lab. ology Viruses, Natl. Inst. Allergy and Infectious Diseases, hesda, MD, 20014); Martin, M. A.; Takemoto, K. K.; wley, P. M.; Aaronson, S. A.; Solomon, D.; Khoury, G. *ology* 90(2): 187-196; 1978.

e role of the human papovavirus BK virus (BKV) in hun neoplasia was evaluated using nucleic acid hybridization l indirect immunofluorescence techniques. None of 12 rmal organ preparations, 5 human tumors, or 16 human nor cell lines was positive for sequences homologous to V DNA. Detectable levels of antibody specific for BKV tumor)-antigen were not found in any of 55 human tumor l lines or in serum samples from any of 67 cancer patients. the basis of these findings, it is unlikely that BKV is nmonly associated with human cancer. (37 refs)

-6906 **Cell Surface Morphology and Adhesive Properties of Normal and Virally Transformed Cells eated with Tunicamycin, an Inhibitor of Protein Glycosyion.** (Eng) Duksin, D. (Dept. Biochemistry, Biological ucture and Medicine, Univ. Washington, Seattle, WA, 195); Holbrook, K.; Williams, K.; Bornstein, P. *Exp Cell s* 116(1): 153-165; 1978.

e effects of tunicamycin (0.1 or 0.2 μg/ml) on the biomical and functional surface properties of mouse 3T3 ls, simian virus 40-transformed 3T3 cells, and polyoma us-transformed 3T3 cells were studied. The cells of all lines came rounded, leaving long attenuated cell processes atched to the substrate. In addition, the nontransformed 3T3 ls showed extensive ruffling of the cell surface and dilation and loss of ribosomes from the rough endoplasmic reticun. There was a marked reduction in all cell lines in a cell rface protein that was similar or identical to fibronectin. nicamycin treatment also resulted in a reduction in the ength of cell adhesion to the substrate, a decrease in plating iciency, and a marked inhibition in the cell spreading rate the surface of the tissue culture plate; the latter two anges were more pronounced in the transformed cells than the nontransformed cells. The data suggest that cell surface ycoproteins, including fibronectin, play a role in determing the surface morphology and adhesive properties of cells. 8 refs)

8-6907 **Mobility of Histones on the Chromosomes of Simian Virus 40.** (Eng) Beard, P. (Swiss Inst. xperimental Cancer Res., CH-1066 Epalinges, Switzernd). *Cell* 15(3): 955-967; 1978.

near simian virus 40 (SV40) chromosomes were prepared *Eco*RI nuclease cleavage of the circular SV40 chromomes released from virions with dithiothreitol at pH 9.8. nromatin-DNA hybrids were constructed with segments of ^{3}H-labeled, naked SV40 DNA covalently joined via the *Eco* RI-generated cohesive ends to segments of linear SV40 chromosome. Upon incubation of chromatin-DNA hybrids at 37 C and moderate ionic strength, histones migrated onto the labeled DNA while retaining the nucleosome structure. This was shown by (1) the pattern of micrococcal nuclease digestion of labeled DNA, (2), by nitrocellulose filter binding of labeled DNA after redigestion of the chromatin-DNA hybrids with *Eco*RI, and (3), by examination of chromatin-DNA hybrids in the electron microscope. Migration was slow, being apparent after several hours. Parallel experiments in which naked DNA and chromosomes were mixed without joining showed no transfer of nucleosomal histone between DNA molecules. The kinetics of *Eco*RI cleavage of the DNA in virion-derived SV40 chromosomes are also consistent with the notion that nucleosomal histones, in the absence of other proteins, can move on DNA. (59 refs)

78-6908 **Influence of Agents Reducing Cell-Substrate Adhesion on Protein and Glycoprotein Patterns of Transformed Mouse Fibroblasts in Culture.** (Rus) Liubimov, A. V. (Lab. Mechanisms Carcinogenesis, Oncology Res. Center, Acad. Medical Sciences, USSR, Moscow, USSR). *Tsitologiia* 20(10): 1179-1185; 1978.

The effect of substances that reduce cell-substrate adhesion (trypsin, EDTA, and urea) on the protein and glycoprotein patterns of methylcholanthrene-transformed mouse fibroblasts (L cells), the serum-free derivative of L cells (LSF), and mouse fibroblasts transformed by simian virus 40 (M-22 cells) was studied by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Incubation with trypsin (10-1,000 μg/ml for 10 min at 37 C) caused no marked changes in the protein and glycoprotein patterns of L cells, but urea (1 mole, 2 hr) and EDTA (200 μg/ml, 2 hr) removed a protein with a mol wt of 240,000. In LSF, trypsin (10 μg/ml, 10 min, 37 C) reduced the level of a 271,000-dalton protein considerably. In M-22 cells, trypsin (1-1,000 μg/ml) caused a protein with a mol wt of 270,000 to disappear. Urea extracted a 270,000-dalton protein nearly completely and a 139,000-dalton protein considerably. EDTA had no marked effect on protein and glycoprotein patterns, but it removed a protein with a mol wt of 270,000. The findings suggest that deficient contact reactions of transformed cells may be due to changes in the pattern and properties of cell components that are sensitive to alterations of adhesion. (7 refs)

78-6909 **Augmented Immunogenicity of Tumor Cell Membranes Produced by Infection with Influenza Virus as Compared to Moloney Sarcoma Virus.** (Eng) Takeichi, N. (Lab. Pathology, Cancer Inst., Hokkaido Univ. Sch. Medicine, Sapporo, Japan); Austin, F. C.; Oikawa, T.; Boone, C. W. *Cancer Res* 38(12): 4580-4584; 1978.

The immunogenicity of tumor cell membranes from Moloney

murine sarcoma virus (MSV)- and influenza virus-infected cells was tested. The tumor-associated transplantation antigens (TATA) of crude membrane extracts from simian virus 40 (SV40)-transformed BALB/3T3 tumor cells lytically infected with influenza virus were much more immunogenic than the TATA of extracts from uninfected cells, as measured by their ability to induce heightened resistance to tumor graft challenge or by heightened lymphocyte-mediated cytotoxicity against tumor cells in vitro. When intact tumor cells (as opposed to membrane extracts) were productively infected with MSV, they became so immunogenic they would only grow in x-irradiated syngeneic animals. However, crude membrane extracts from the MSV-infected tumor cells showed no increase in TATA activity analogous to that seen after infection with influenza virus. Thus, influenza virus augmentation of tumor membrane TATA may be different from the oncornavirus augmentation of intact tumor cell TATA reported previously. It appears that MSV and, possibly, other oncornaviruses cannot be used to augment the TATA activity of tumor cell membranes in the same way that other surface-budding viruses can. (25 refs)

78-6910 **Simian Virus 40 *A* Gene Function: DNA Content Analysis of Chinese Hamster Cells Transformed by an Early Temperature-sensitive Virus Mutant.** (Eng) Robinson, C. C. (Dept. Pathology, Univ. Colorado Medical Center, 4200 E. Ninth Ave., Denver, CO, 80262); Lehman, J. M. *Proc Natl Acad Sci USA* 75(9): 4389-4393; 1978.

Replication of Chinese hamster embryo cell lines (ChH WT-2, ChH A58, and ChH A58-1) transformed by wild-type simian virus 40 (WT SV40) and the SV40 temperature-sensitive *A* gene mutant (*tsA*58) was examined by flow microfluorometry and autoradiography of ^{3}H-thymidine-labeled cells to determine whether DNA synthesis in transformed cells is initiated by the *A* gene. At the permissive temperature (37 C), the *tsA*58-transformed cells resembled the WT transformants in cell morphology, colony formation, high saturation density, and rapid replication. They seemed to revert to a normal phenotype at the nonpermissive temperature (40.5 C). However, flow microfluorometric analysis of the cell DNA content at 40.5 C showed that under conditions in which normal embryo cells enter a resting state, the *tsA*58 transformants continued to replicate. The low density of the cultures was maintained by a balance among cell proliferation, cell death, and sloughing of dead cells into the culture medium, and it did not represent a return to normal growth. Thus, loss of the phenotypic characteristics of transformation cannot be explained by arrest of the cells in the G_1 (G_0) phase of the cell cycle. It is suggested that the initiator hypothesis for the function of the *A* gene product in the maintenance of transformation must be reevaluated. (34 refs)

78-6911 **Suppressive Effects on Simian Virus 40-induced Oncogenesis of Several Immunosuppressive Agents and Hormonal Modifications Applied During the I tent Period.** (Eng) Ohtaki, S. (Dept. Pathology, Nalt. In Health, Tokyo Gakuen 4-7-1, Musashi-Murayama, Tok 190-12, Japan). *Cancer Res* 38(12): 4698-4710; 1978.

Host factors affecting tumorigenesis at different stages, esp cially before and after the appearance of tumor cells, we studied in two experiments: (1) simian virus 40 (SV40)-i duced oncogenesis in Syrian golden hamsters, to investiga the latent period; and (2) transplantation of homologous, p mary SV40 tumor cells into hamster, to investigate a la stage of tumorigenesis. The mean latent period for SV40 t mor induction was about 6 wk shorter in female hamste than in males ($p < 0.02$). The mean latent period in c phorectomized females was 12.6 wk longer than that in int females. In contrast, tumor development was not significa ly affected by orchiectomy. Estrone treatment (0.2-0.3 m sc) at birth delayed tumor development significantly in bo sexes. Tumor development was significantly accelerated testosterone treatment (0.5 mg, sc) of males at age 15 wk, t mean latency period being decreased by 11 wk. By each these hormonal modifications, growth of transplanted SV tumors was influenced in a different way from that of tum induction. Immunosuppressive treatments, such as thyme tomy or administration of antilymphocyte sera, cycloph phamide, or cortisone acetate, delayed and decreased tum development when applied in the latent period, and the d gree or pattern of this effect varied from one procedure another, depending on the sex and age of the animals. contrast, tumor growth was markedly accelerated in thyme tomized or cortisone-treated hosts of either sex. The differe and almost reverse effect of the same procedures in the tw phases of tumorigenesis indicates that two distinct mec anisms may be operating during these phases. The differe effect may be due to the absence of "mature" neoplastic ce in the latent period, except for a few weeks before the appea ance of a palpable tumor. These results suggest that the lo latency period may be needed for completion of SV40-i duced neoplastic conversion of cells. (47 refs)

78-6912 **Simian Virus 40 Production After Viral Uncoa ing in the CV-1 Cell Nucleus.** (Eng) Gershey, L. (Rockefeller Univ., New York, NY, 10021); Diacumako E. G. *J Virol* 28(1): 415-416; 1978.

A normal yield of infectious simian virus 40 was produc by a culture of African green monkey kidney CV-1 cells aft a few cells were inoculated with an av of one particle plaque-purified virus per nucleus by microinjection. (7 ref

78-6913 **Simian Virus 40 DNA Replication in Isolate Replicating Viral Chromosomes.** (Eng) Su, R. (Dept. Microbiology, Univ. Kansas, Lawrence, KS, 66044 DePamphilis, M. L. *J Virol* 28(1): 53-65; 1978.

Three soluble subnuclear systems (nuclear extracts, nucle

rotein complexes, and replicating chromosomes prepared om simian virus 40-infected CV-1 cells) were studied to etermine the minimum conditions necessary for DNA re- ication in vitro. DNA synthesis was measured with and ithout CV-1 cell cytosol in the reaction mixture. With nu- ear extracts, cytosol stimulated total DNA synthesis (2-3 nes), elongation of nascent DNA chains, maturation and ining of Okazaki pieces (transient intermediates), and the nversion of replicating viral DNA into covalently closed, perhelical DNA. The response of nucleoprotein complexes as similar but often 10%-30% lower. In contrast, isolated plicating chromosomes in the presence of cytosol appeared ily to complete and join Okazaki pieces on the DNA tem- ates. They failed to extend nascent DNA chains prelabeled vivo with ^{3}H-thymidine or labeled in vitro with α-^{32}P-deox- ytosine triphosphates (α-^{32}P-dCTP). Consequently, the nversion of viral replicating DNA into mature DNA was ven to eight times less than that observed in nuclear ex- acts. In the absence of cytosol, Okazaki pieces were still beled with α-^{32}P-dCTP in vitro, but completely failed to join the growing nascent DNA chains, demonstrating the re- uirement of cytosol factors at this stage in DNA elongation. reatment of nucleoprotein complexes with 0.6-2.0 M NaCl sulted in complete loss of endogenous DNA synthesis and lack of response to cytosol. These results demonstrate that ntinuation of endogenous DNA replication in vitro re- uires both the soluble cytosol fraction and a complex nucleo- rotein template whose ability to continue DNA synthesis epends on its concentration and ionic environment during s preparation. (31 refs)

78-6914 **Non-Coordinate Expression of SV40 Transformation in Cell Hybrids (Meeting Abstract).** Eng) Howell, N. (Sidney Farber Cancer Inst., Boston, MA, 2115); Sager, R. *J Cell Biol* 79(2, part 2): 396a; 1978. (no efs)

78-6915 **SV40-transformed Hamster Cells Resistant to 100-250 μg/ml of Ethidium Bromide.** (Eng) Wolf, G. (Max-Planck-Institut fur Virusforschung, 7400 Tu- ingen, W. Germany); Tejmar, L.; Borell, S.; Klietmann, W. *Cell Sci* 33: 157-169; 1978.

imian virus 40 (SV40)-transformed hamster cells selected or resistance to ethidium bromide (EB, 100-250 μg/ml) were haracterized. EB resistance was maintained during propaga- on in EB-containing medium and thus seemed to be geneti- ally determined. The EB-resistant cells were considerably ss tumorigenic in Syrian golden hamsters than wild-type ells. They had a normal ultrastructure, except for a highly ondensed conformation of the mitochondrial cristae. Unlike ild-type cells, the resistant cells showed no significant inhi- ition of mitochondrial DNA synthesis in the presence of 16 g/ml EB. The polypeptides of the mitochondrial fractions f wild-type and resistant cells were significantly different: polypeptide 14, which was present in wild-type cells, was absent or greatly reduced in the mitochondria of the resistant cells, and the relative proportions of polypeptides 1:2 and 7:8:9 were different. The mechanism of EB resistance in mammalian cells has not been determined. (27 refs)

78-6916 **Simian Virus 40 T Antigen Binds to Host Cell Chromosomes.** (Eng) D'Alisa, R. M. (Rockefeller Univ., New York, NY, 10021); Gershey, E. L. *Nature* 274(5667): 164-166; 1978.

The binding of simian virus 40 (SV40) T antigen to mammalian chromosomes was studied using a fibroblastic cell strain derived from a male Indian deer, *Muntiacus muntjak*, an animal with only seven chromosomes, which can be unequivocally identified. Cultured muntjac cells were infected with SV40 strain VA 4554 at multiplicities between 200 and 500 plaque-forming units/cell. Seventy-two hours after infection, the chromosomes were swollen in 0.075 M KCl for 12 min, fixed in 3:1 methanol:acetic acid, air-dried, and stained for T antigen by indirect immunofluorescence. The preparations were photographed on an inverted microscope. Alternatively, cells were grown in glass slides and arrested with colcemid before KCl treatment and fixation. No differences in chromosome morphology were detected with the two methods. T antigen was associated with all chromosomes, including the small Y, of infected cells. The binding appeared to be specific for the fluorescent chromosomes of infected cells, since uninfected cells did not contain fluorescent chromosomes and (2) presumably uninfected cells within the SV40-treated population also did not fluoresce. The similarity of the T-antigen binding patterns to Q- and G-banding patterns suggests that the antigen binds to initiation sites for host cell DNA replication. (27 refs)

78-6917 **Definition of the Boundaries of the Origin of DNA Replication in Simian Virus 40.** (Eng) Subramanian, K. N. (Dept. Microbiology, Univ. Illinois Medical Center, Chicago, IL, 60612); Shenk, T. *Nucleic Acids Res* 5(10): 3635-3642; 1978.

Using DNA sequencing techniques, the exact location of the deletion in *dl* 892, a viable deletion mutant of simian virus 40 (SV40) reported to map very near the unique replication origin of SV40, was determined. Autoradiographic studies showed that *dl* 892 lacks a segment of 19 nucleotides (located between positions 187 and 205 in the *Eco* RII-G sequence, both inclusive) present in wild-type SV40 DNA. In view of the fact that segments of DNA occurring distal position 186 could be deleted without affecting the replication of the viral DNA (and the ability of the virus to grow without a helper), one of the boundaries for the replication origin located distal to the *Hind* (11 + 111) -A-C junction could be placed at position 186. Previous studies indicate that sequences to the left of map position 0.660 are not needed for initiation of

SV40 DNA replication. Therefore, the other boundary of the replication origin has been placed at map position 0.660 corresponding to the *Hae* III restriction site at nucleotide 102 in the *Eco* RII-G sequence. Thus, according to the present estimate, the SV40 replication origin consists of a max of 85 nucleotides located between positions 102 and 185 in the sequence of the *Eco* RII-G fragment derived previously. This sequence includes the 27-nucleotide perfect palindrome, the 17-nucleotide "true" palindrome (containing a single imperfection in its sequence), the 17-nucleotide A-T-rich sequence, and the 15-nucleotide imperfect palindrome, all shown to be present in the previously derived *Eco*RII-G sequence. These and previous results have enabled the boundaries of the replication origin to be narrowed down to 85 nucleotides within the sequence of SV40. (10 refs)

78-6918 **The Detection and Characterization of Multiple Forms of SV40 Nucleoprotein Complexes.** (Eng) Garber, E. A. (Dept. Biochemical Sciences, Princeton Univ., Princeton, NJ, 08540); Seidman, M. M.; Levine, A. J. *Virology* 90(2): 305-316; 1978.

Using a newly developed method for extracting multiple forms of simian virus 40 (SV40) nucleoprotein complexes from the nuclei of virus-infected cells, the production and maturation of the SV40 chromosome in vivo were studied. Four different forms of SV40 DNA-protein complexes were identified: a heterogeneous (75S to 200S) replicative intermediate; a 75S minichromosome; a 200S previrion particle; and a mature virion (250S). After replicating in the heterogeneous 75S to 200S complexes, the newly replicating chromosome appeared to be converted to the 75S form, which matured into the 200S previrion structure. By 45 to 60 min, mature virions were observed. The sequence of appearance of these complexes was suggestive of a precursor-product relationship. The data demonstrated that 90% of the viral DNA was encapsulated by 4 hr after its synthesis. (25 refs)

78-6919 **Identification of Oncogenic Chromosomes in Transformed Human Cells.** (Eng) Croce, C. M. (Wistar Inst. Anatomy and Biology, 36th and Spruce Sts., Philadelphia, PA, 19104). *In: Neoplastic Transformation: Mechanisms and Consequences. Proceedings of a meeting held by the Dahlem Workshop on Neoplastic Transformation: Mechanisms and Consequences in Berlin, May 9-13, 1977.* Dahlem Workshop on Neoplastic Transformation: Mechanisms and Consequences (Berlin, W. Germany): 314 pp.; 69-85; 1977.

To determine whether viral DNA sequences are associated with specific chromosomes in transformed cells and whether integrated viral DNA sequences are responsible for expression of the transformed phenotype and malignancy, a large number of somatic cell hybrids between rodent cells and different simian virus 40 (SV40)-transformed human cells w produced and investigated. Three independent SV40 T-an gen-positive hybrid clones between CT1D mouse cells a LN-SV SV40-transformed human cells were subcloned, a the subclones were analyzed for the expression of SV40 tum antigen and the presence or absence of human chromoso 7. Somatic cell hybrids between thymidine kinase-deficie IT-22 mouse or A3 hamster cells and GN54VA transform human fibroblasts were also studied. The results showed th the SV40 genome can be integrated in at least two differe human chromosomes: 7 and 17. These and further stud demonstrated that it was possible to map the integration si of oncogenic viruses in virus-transformed human cells a to identify the human chromosomes responsible for t expression of malignancy by somatic cell hybridization. Sin these chromosomes can be isolated on a normal inbred mou strain background, it should also be possible to elicit humo and cellular immunoresponses to human tumor-associat antigens using hybrid cells. (26 refs)

78-6920 **The Sequences between 0.59 and 0.54 M Units on SV40 DNA Code for the Unique R gion of Small t Antigen.** (Eng) Paucha, E. (Translation La Imperial Cancer Res. Fund, London WC2A 3PX, Englan Smith, A. E. *Cell* 15(3): 1011-1020; 1978.

The hypothesis that the carboxy terminal portion of simi virus 40 (SV40) small t antigen is encoded by a sequence nucleotides from the region between 0.59-0.54 map units SV40 DNA was tested by characterizing the putative sho ened forms or fragments of small t produced by SV40 m tants (dl 884, dl 885, dl 890) with deletions in this genor region. Attempts to isolate the putative fragments of sm t from mutant-infected cells, or from cell-free systems prim with messenger RNA (mRNA) from mutant-infected cel resulted in only low yields of the fragments. Experimer using purified SV40 mRNA in low background cell-free sy tems, in which large T and small t could be detected witho immunoprecipitation, suggested that these low yields we due to the reduced amounts of mRNA coding for the sho ened forms of small t present in the mutant-infected cel Larger amounts of putative fragments of small t were pr duced by translation of deletion mutant complementa RNA (synthesized in vitro using purified deletion muta DNA and *Escherichia coli* RNA polymerase). Fingerpri analysis of the proteins produced showed that they contain most, if not all, of the methionine peptides common to sma t and large T. Furthermore, the fragments of small t produce in response to dl 884 and dl 890 lacked two methionine pe tides that were present in small t but not in large T. The results provide direct evidence that the region betwe 0.59-0.54 map units on SV40 DNA codes for polypeptic sequences that are unique to small t, and they establish th the nucleotide sequences from this region are both a codi sequence (for small t) and an intervening sequence (for lar T). (38 refs)

78-6921 **Selective Degradation of Newly Synthesized Nonmessenger Simian Virus 40 Transcripts.** (Eng) Chiu, N. H. (Lab. Biology Viruses, Natl. Inst. Allergy and Infectious Diseases, NIH, Bethesda, MD, 20014); Radonovich, M. F.; Thoren, M. M.; Salzman, N. P. *J Virol* 28(2): 590-599; 1978.

Under pulse-chase conditions with glucosamine, the processing, transport, and degradation of a relatively homogeneous population of nuclear viral RNA molecules (nvRNA) labeled during a brief pulse were examined 45 hr postinfection. By pretreating the simian virus 40-infected BSC-1 cells with glucosamine, ^{3}H-uridine labeling of cellular and viral RNA could be halted immediately by the addition of cold uridine. Both messenger and nonmessenger regions of the late strand were transcribed during the 5-min labeling period and, after various chase periods, nvRNA's that sedimented at 16S, 17.5S, and 19S were observed. The fraction of the late strand that did not give rise to stable late messenger RNA (50% of nvRNA) was degraded rapidly, with a half-life of 8 min. A 40% fraction was transported to the cytoplasm, and the remaining 10% was sedimented from the nucleus at 2S-4S. These 2S-4S nvRNA's had a half-life of 3 hr, and hybridization studies suggested that they were partly coded for by the late-strand nonmessenger region and were derived from the initial nuclear processing step. Another part was coded for by the late-strand messenger region and may result from cleavage of 19S RNA into 17.5 and 16 S RNA's. Transport of nvRNA into the cytoplasm was detected after a 5-min pulse and a 7-min chase. Accumulation in the cytoplasm was max after a 30-min to 1-hr chase. At least two viral cytoplasmic species were noted: 19S (half-life 2 hr), which is likely transported directly from the nucleus, and 16S (half-life 5 hr), which may be formed by cleavage of the larger species in the nucleus and/or cytoplasm. (31 refs)

78-6922 **Does Simian Virus 40 DNA Integrate into Cellular DNA During Productive Infection?** (Eng) Rigby, P. W. (Dept. Biochemistry, Imperial Coll. Science and Technology, London SW7 2AZ, England); Berg, P. *J Virol* 28(2): 475-489; 1978.

The possibility that simian virus 40 (SV40) DNA becomes covalently integrated into the chromosomal DNA of productively infected cells was investigated by isolating and purifying SV40 DNA late after infection of African green monkey kidney cells. This fraction contained large amounts of SV40 DNA sequences, but their behavior in electron microscope and restriction endonuclease mapping experiments indicated that most, if not all, of the viral DNA was not covalently joined to cellular DNA. Instead, it was organized into large, tandem, head-to-tail polymeric structures of wholly viral origin. The results showed that heteroduplexes between high-mol-wt SV40 DNA and a mutant SV40 DNA probe were not formed unless the former was digested with *Eco*RI or *Hpa*II, enzymes that cleave SV40 DNA once. The electrophoretic mobility of the high-mol-wt SV40 DNA was not perceptibly altered by digestion with several restriction endonucleases that cleave cellular DNA but not SV40 DNA. However, digestion with *Eco*RI, *Hpa*II, *Kpn*I, or *Taq*I converted all the SV40 DNA into unit-length, linear molecules. The high-mol-wt SV40 DNA was highly infectious in the standard plaque assay, and this infectivity was increased by digestion with *Eco*RI or *Hpa*II. Because the polymers appeared upon extensive replication of the viral DNA and homopolymers were produced after coinfections with two physically distinguishable SV40 genomes, it is concluded that they are synthesized by a replicational mechanism. Although the data cannot exclude a low level of SV40 DNA integration during productive infection, sedimentation criteria used previously to demonstrate integration are misleading because novel forms of viral DNA, which copurify with cellular DNA, mimic integrated genomes. (46 refs)

78-6923 **Presence of Histone H1 in the Chromosome of SV40 Virions Isolated from the Nuclei of Infected Cells.** (Rus) Nedospasov, S. A. (Inst. Molecular Biology, Moscow, USSR); Bakaev, V. V.; Georgiev, G. P. *Dokl Akad Nauk SSSR* 241(2): 485-487; 1978.

The isolation of virions of simian virus 40 (SV40) from infected CV-1 monkey cells is described. Cells were incubated with ^{3}H-thymidine (2 μCi/ml) and ^{14}C-amino acids (5 μCi/ml) for 72 hr, washed, and centrifuged; the supernatant was then centrifuged in a sucrose gradient. The DNA radioactivity curve contained two distinct peaks, one 60S and the other at 200S. The peaks of protein radioactivity coincided with the peaks of DNA radioactivity. Electron microscope analysis of material from each peak showed that the light peak contained particles with a diameter (approx 250 A) that corresponded to that of the native compact form of free SV40 minichromosomes. The heavy peak contained typical mature SV40 virions (420-450 A in diameter) with clearly visible capsomers. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis detected all five histones (including histone H1) in both the free minichromosomes and the virion particles. The ratio of histone H1 to the other histones was stoichiometric (1 molecule of H1/nucleosome). These findings indicate that the mature virus particle contains a chromosome that is extremely similar to the chromosome of the eukaryotes. (13 refs)

78-6924 **Expression of Simian Virus 40 Early Genes in Transformed Rat Cells is Correlated with Maintenance of the Transformed Phenotype.** (Eng) Gaudray, P. (Centre de Biochimie, Universite de Nice, Parc Valrose, 06034 Nice, France); Rassoulzadegan, M.; Cuzin, F. *Proc Natl Acad Sci USA* 75(10): 4987-4991; 1978.

Experiments that show a clear temperature-dependence of the synthesis of all the immunoprecipitable tumor (T) antigenic polypeptides in the temperature-sensitive *A-N* (*tsA-N*)

simian virus 40 (SV40) transformants, but not in *tsA-A* SV40 transformants, are presented. Early viral polypeptides synthesized in SV-transformed FR 3T3 rat fibroblasts were identified by immunoprecipitation using anti-T antigen immune serum. Four polypeptide classes were identified, none of which was detectable in extracts of nontransformed cells or precipitated from transformed cell extracts by nonimmune serum. Their apparent mol wts were 92,000, 63,000, 56,000, and 19,000 daltons. A similar pattern was observed in extracts from lytically infected cells, but there was a reproducible quantitative difference between the relative amounts of immunoprecipitable polypeptide species in lytic and transformed cell extracts: the middle T 56,000- and 63,000-dalton species amounted to 5%-8% of the total T antigen-associated radioactivity in lytic cell extracts, compared with 20%-30% in transformed cells. It appears unlikely that these components result from random proteolysis or any other chemical modification in extracts. Previously reported evidence suggests that these middle T polypeptides may represent virus-coded polypeptides, produced by translation of independent spliced messenger RNA's or by post-translational processing of a larger viral polypeptide (large T); alternatively, they may be cellular gene products in a specific and stoichiometric association with viral proteins. In ^{35}S-methionine-labeled *tsA*30-*A* transformants, which maintain the transformed phenotype at high temperature, only minor quantitative variations in the pattern of T antigen synthesis were observed when the cultures were shifted from 33 C to 40.5 C. In contrast, the labeling rate of the four virus-specific polypeptides decreased by 90% or more at the high temperature in the *tsA-N* transformants. In all cases, a coordinated variation of the radioactivity associated with the different polypeptide classes was observed. These results suggest that the synthesis and/or processing of early viral proteins is controlled by different mechanisms in various types of SV40 transformants, and that it may be under the positive control a virus-coded protein in transformed N cells. (32 refs)

78-6925 **Neoplastic Transformation of Permissive Monkey Cells by Subgenomic Fragments of SV40 DNA and Rescue of SV40 Virions from Transformed Cells by Cell Fusion.** (Eng) Moyer, R. C. (Thorman Cancer Res. Lab., Trinity Univ., San Antonio, TX, 78284); Moyer, M. P.; Gerodetti, M. H. *In: Prevention and Detection of Cancer. Proceedings of the Third International Symposium on Detection and Prevention of Cancer Held by the International Study Group for the Detection and Prevention of Cancer in New York, April 26 - May 1, 1976.* International Study Group for the Detection and Prevention of Cancer. (New York, NY): Vol. 2 Part 1), 2404 pp.; 1443-1464; 1978.

The *Eco*RI/*Hap* A fragment of simian virus 40 (SV40) DNA, which comprises 74% of the viral genome including the early region, and the *Eco*RI/*Hap* B fragment, which comprises 26% of the genome including most of the late regions, were tested for their ability to transform permissive TC7/CV-1 monkey cells. The two fragments were separated by electrophoresis and added to cell cultures in the presence of di thylaminoethyl-dextran. Results of indirect immunofluore cence tests revealed that either fragment transformed the cel without evidence of cytopathology or V antigen. Cells tran formed by the 74% fragment displayed SV40 T antigen an were tumorigenic in newborn hamsters, but cells transforme by the 26% fragment appeared to express a new antigen an were not tumorigenic. Fusion of cells transformed by bot types of fragments resulted in SV40 cytopathology and antigen production, which indicated that the two defecti provirus complements were rescued to produce infectious v rions. An "alien DNA" hypothesis is proposed to accoun for virus-induced and other forms of neoplasia. (61 refs)

78-6926 **Growth Control in Simian Virus 40-transforme Rat Cells: Temperature-independent Expressio of the Transformed Phenotype in *tsA* Transformants Derive by Agar Selection.** (Eng) Rassoulzadegan, M. (Centre de Bio chimie, Universite de Nice, Parc Valrose, 06034 Nice France); Perbal, B.; Cuzin, F. *J Virol* 28(1): 1-5; 1978.

Fischer rat fibroblasts (FR 3T3) were infected with a temper ature-sensitive simian virus 40 (SV40) mutant (*tsA30*) usin transformed lines isolated from foci (*tsA30*-N) or from colo nies grown in soft agar (*tsA30*-A). All (4/4) of the *tsA-A* transformants expressed the transformed phenotype at 40.5 C, but 2/3 *tsA*-N lines were temperature dependent for al the transformation characteristics studied. The pattern o temperature-dependent vs temperature-independent mainte nance in these transformants thus appears similar to tha found previously for transformed lines isolated after infectio with polyoma virus *tsA* mutants. Temperature-shift experi ments fused to CV-1 monkey cells indicated that al the *tsA*-A transformants carry mutant endogenou viral genomes. SV40 tumor antigen could be detecte by immunofluorescence in all of the transformant at 33 C. Two distinct patterns of immunofluorescen staining were seen: all transformants of *tsA*-A show ed homogeneous nuclear staining, but all the *tsA*-N showed a heterogeneous pattern. These rusults sugges that distinct modes of regulation of tumor antige synthesis might be associated with the A and N mechanism of transformation. (18 refs)

78-6927 **Mapping of Early SV40-Specific Functions by Microinjection of Different Early Viral DNA Fragments.** (Eng) Mueller, C. (Institut fur Molekularbiologi und Biochemie, Freien Universitat Berlin, W. Berlin 33, Ar nimallee 22, Germany); Graessmann, A.; Graessmann, M *Cell* 15(2): 579-585; 1978.

The ability of simian virus 40 (SV40) DNA fragments con taining 60%-100% of the early genome region to induce early virus-specific functions in monkey and mouse kidney cell was studied. The following early virus-specific events were

etected 24 hr after microinjection of SV40 DNA I or its in itro transcript, cRNA complementary to the early viral NA strand: intranuclear tumor (T) antigen and U antigen ccumulation; stimulation of cellular DNA synthesis; initiaon of late SV40 gene expression; and induction of adenovius 2 fiber protein synthesis. Proteins with T antigenicity ere efficiently synthesized in cells after microinjection of ny of the four SV40 DNA fragments sharing a common end t about 0.73 map unit and containing 58%-100% of the arly genome. Cells injected with fragment Bgl I/Bam HI-A, hich contains 100% of the early genome, were T-antien-negative. Only the full-length early fragment Hpa II/Bam HI-A induced the remaining early SV40-specific funcions. The data indicate that only an intact early viral protein an stimulate both viral and cellular DNA synthesis, DNA equences at map position 0.67 being required for intracellur early viral transcription. (41 refs)

78-6928 **Transforming Viruses Directly Reduce the Cellular Growth Requirement for a Platelet Derived Growth Factor.** (Eng) Scher, C. D. (Dept. Pediatrics, Sidney Farber Cancer Inst., Boston, MA, 02115); Pledger, W. J.; Martin, P.; Antoniades, H.; Stiles, C. D. *J Cell Physiol* 97(3, part 1): 371-380; 1978.

The ability of early passage mouse embryo fibroblasts, mouse 3T3 cells, early passage diploid human fibroblasts, and 3T3 cells and human fibroblasts transformed by simian virus 40 (SV40) or retroviruses to grow in medium supplemented with defibrinogenated platelet-poor plasma (PPP) was studied. The untransformed cells grew to higher cell densities in medium supplemented with serum than in medium supplemented with PPP. However, the human fibroblasts displayed this differential growth response only in the presence of hypophysiologic concentrations of calcium. When heated (100 C) extracts of human platelets were added to PPP-supplemented medium, growth of human and mouse embryo fibroblasts was the same as that in serum-supplemented medium. Fibroblasts transformed with SV40 or retroviruses grew to the same densities in medium supplemented with serum of PPP. Infection of BALB/c-3T3 cells with SV40 rapidly induced them to grow in PPP medium, whereas 3T3 cells infected but not transformed by retroviruses did not replicate in PPP medium. Cells that did not proliferate well in PPP medium did not form tumors when inoculated into athymic nude mice, whereas many of the lines that grew well in PPP medium were tumorigenic in nude mice.

78-6929 **Another Chromosomal Assignment for a Simian Virus 40 Integration Site in Human Cells.** (Eng) Kucherlapati, R. (Dept. Biochemical Sciences, Princeton Univ., Princeton, NJ, 08540); Hwang, S. P.; Shimizu, N.; McDougall, J. K.; Botchan, M. R. *Proc Natl Acad Sci USA* 75(9): 4460-4464; 1978.

Hybrid cell lines between B82, a murine cell line deficient in thymidine kinase (TK), and GM637, a simian virus 40 (SV40)-transformed human fibroblast cell line, were analyzed for SV40 T antigen (T-ag), V antigen (V-ag), and integrated viral DNA. Total high-mol wt DNA from GM637 was separated from free viral DNA by sucrose gradient fractionation and agarose gel electrophoresis. This high-mol-wt DNA was hydrolyzed with restriction endonuclease *Ball*, and SV40 DNA was detected by blot hybridization. Only one band containing SV40 DNA was consistently noted in GM637 and eight other hybrid cell DNA preparations, all of which were T-ag-positive. Cells lacking this viral DNA band were all T-ag-negative. Indirect immunofluorescence studies failed to show a correlation between the presence of T-ag and the human TK gene, which is located on chromosome 17, indicating that SV40 was not integrated on human chromosome 17. Likewise, none of the 16 gene markers tested, representing 14 different chromosomes, correlated with the presence of T-ag. Chromosome analyses of 20 B82/GM637 hybrid cell lines showed that, with one exception, the only chromosome present in all T-ag+ cell hybrids was chromosome 8. All hybrids that were T-ag+ had a single band of DNA that hybridized with SV40 DNA and migrated to the same position in all hybrids, indicating that the position of the viral sequences in the hybrids was stable. These data and those of earlier studies indicate that SV40 can integrate at one of several sites in the human genome and that this process is not chromosome specific. (30 refs)

78-6930 **Viable Deletion Mutants in the Simian Virus 40 Early Region.** (Eng) Feunteun, J. (Institut de Recherches Scientifiques sur le Cancer, B.P. no. 8, 94800-Villejuif, France); Kress, M.; Gardes, M.; Monier, R. *Proc Natl Acad Sci USA* 75(9): 4455-4459; 1978.

Simian virus 40 (SV40) mutants that have lost the unique site for the restriction enzyme *Taq* I at 0.565 were developed in monkey CV-1 cells in order to isolate *hr-t*-like SV40 mutants. Purified *taq* I linear SV40 DNA (50 μg/ml) was exposed to λ 5′-exonuclease (20 μg/ml) at 0 C for 30 min in 67 mM glycinate buffer, pH 9.4/2.5 mM $MgCl_2$, and then used for plaque assay on CV-1 cells. Five *Taq* I-resistant clones were purified, and DNA from each was prepared for restriction enzyme analysis using *Hin*dIII, *Hin*fI, *Alu* I, and *Hae* III. Two deletion classes were seen, both located at 0.565 on the genome. One deletion was approx 20-30 base pairs long, the other approx 250-310 base pairs long. To characterize the T antigens present in these deletion mutants, CV-1 cells infected with the mutants were labeled for 3 hr with ^{35}S-methionine and subjected to immunoprecipitation followed by gel electrophoresis. No difference was noted between any of the mutants and wild-type large T antigen. Wild-type small t antigen (t-ag), however, was missing from the mutants; in four mutants it was replaced by new polypeptides of mol wt 18,500, 17,000, 16,500, and 12,500 in greatly reduced quantities. In the fifth mutant, no t-ag of any type was detectable. The low yield of t-ag antigen was not due to a rapid turnover, and in

mixed infections the respective yields of wild-type and mutant t-ag were as expected. Thus, the deletions affect a region that is part of the t-ag coding sequences, but not those of large T antigen. Like *hr-t* polyoma mutants, the transforming ability of these cells, as measured by growth induction in agar, was clearly altered. A second complementation group in the SV40 early region is therefore defined by virtue of the fact that these mutants can complement a *tsA* mutant for transformation. (27 refs)

78-6931 **Are the SV40 Induced Antigens and the Morphology of SV40 Transformed Cells Correlated (Meeting Abstract)?** (Eng) Weller, N. K. (Dept. Molecular, Cellular and Developmental Biology, Univ. Colorado, Boulder, CO). *J Cell Biol* 79(2, part 2): 405a; 1978. (no refs)

78-6932 **Regulation of SV40 T Antigen in SV40 Transformed Mouse Cells (Meeting Abstract).** (Eng) Axelrod, H. R. (Dept. Biochemistry, Princeton Univ., Princeton, NJ); Levine, A. J. *J Cell Biol* 79(2, part 2): 401a; 1978. (2 refs)

78-6933 **Induction of Infectious Virus DNA and Virus Particles by Mitomycin C in SV40-Transformed Mouse Cells.** (Eng) Lavialle, C. (Institut de Recherches Scientifiques sur le Cancer, B.P. No. 8, 94800-Villejuif, France); Suarez, H. G.; Morris, A. G.; Cassingena, R. *J Gen Virol* 41(1): 201-205; 1978.

The efficiency of mitomycin C (MC) in inducting simian virus 40 (SV40) in nonpermissive mouse cells was investigated. Following infection of 3T3-4E Swiss mouse cells with SV40 (multiplicity of infection, 100 plaque-forming units/cell), an SV40-transformed cell line (SV/3T3-4E) was isolated and four independent clones were derived. The parental line and three of the clones (1,2, and 4) spontaneously produced small amounts of infectious virus DNA but treatment of these cells with MC (0.3-3.0 μg/ml) enhanced the yield of virus DNA 10- to 100-fold. Infectious virus particles, never detected in untreated cultures, were occasionally induced by MC in the parental line and in clones 1, 2 and 4. A correlation was found between the level of SV40 DNA inducibility of a given clone and its capacity to produce virions in detectable amounts after MC treatment. It is concluded that SV/3T3-4E cells contain small amounts of free infectious SV40 DNA and that most cells in the parental line are capable of producing SV40 DNA spontaneously. (16 refs)

78-6934 **Genetics of SV40 T-Antigen Expression: Studies of Twins, Heritable Syndromes and Cancer Families.** (Eng) Blattner, W. A. (Environmental Branch, NCI, Bethesda, MD, 20014); Lubiniecki, A. S.; Mulvihill, J J.; Lalley, P.; Fraumeni, J. F. *Int J Cancer* 22(3): 231-238 1978.

The susceptibility of human skin fibroblasts to simian viru 40 (SV40) infection has been suggested as a marker of higl risk for leukemia and, possibly, other cancers. To search fo a pattern of genetic transmission, fibroblasts from 9 pairs o identical twins (in 7 pairs, one co-twin had acute leukemia in 1, both had aplastic anemia) and from 129 members of 2(cancer-prone families (including 16 members with cancer were tested for SV40 tumor (T) antigen expression (SVTAE in a 3-day immunofluorescence assay. The variance of T-anti gen values was significantly less in identical than in fraterna twins or nontwin sibs (taken from cancer-prone or contro families), suggesting a heritable component in the regulatior of SV40 infection. In the families, SV40 T-antigen values o parents and children, as determined in the fibroblast im munofluorescence assay, were compared to models of Men delian inheritance. At least three modes of inheritance, au tosomal dominant, recessive, and x-linked, were observed There was a tendency for offspring values to be distributed unimodally with respect to parental values. With the excep tion of Fanconi's anemia, the values for patients with cancer or predisposing syndromes were not elevated uniformly. The findings suggest that the genetic regulation of T-antigen expression is complex and, since no one pattern clearly predominates, probably accounts for a lack of disease effect of SVTAE. Thus, the utility of SVTAE as a marker of cancer risk appears limited. (35 refs)

78-6935 **Quantitative Correlation Between Simian Virus 40 T-Antigen Synthesis and Late Viral Gene Expression in Permissive and Nonpermissive Cells.** (Eng) Graessmann, A. (Institut fuer Molekularbiologie und Biochemie, Freien Universitaet Berlin, W. Berlin 33, W. Germany); Graessmann, M.; Guhl, E.; Mueller, C. *J Cell Biol* 77(1) R1-R8; 1978.

The intranuclear synthesis and accumulation of simian virus 40 (SV40) tumor (T) antigen was investigated by immunofluorescence and cytofluorometry in permissive CV1 monkey cells and nonpermissive 3T3 mouse cells at different times after infection. CV1 cells accumulated T antigen continuously over a 48-hr period after infection, whereas in 3T3 cells the T-antigen content remained constant and at a comparatively low level. Only those CV1 cells that had attained a threshold concentration of intranuclear T antigen [28 arbitrary units (AU)] synthesized viral capsid proteins (V antigen). Nearly 100% of nonpermissive 3T3 cells infected with 500 plaque-forming units of SV40 became T-antigen positive at 65 hr postinfection, but V antigen was not detected at any time. The minimum T-antigen threshold value (52 AU) for V-antigen synthesis in the nonpermissive cells was attained by microinjecting the cells with large amounts of SV40 DNA. The 3T3 cells may synthesize T antigen less efficiently and/or degrade it at a higher rate than monkey cells. Since the in-

nuclear presence of at least 250-500 viral particles or viral NA molecules overcomes nonpermissiveness, an early ent in the infectious cycle (adsorption, penetration, in- cellular release) must be involved in the nonpermissive pe of response in infected mouse cells. (23 refs)

-6936 **Studies of Simian Sarcoma and Simian Sarcoma-associated Virus. II. Isolation of the Ma- Viral Glycoprotein, Properties of This Component and Specific Antiserum.** (Eng) Thiel, H. J. (Dept. Surgery, ke Univ. Medical Center, Durham, NC, 27710); Beug, H.; af, T.; Schwarz, H.; Schafer, W.; Bergholz, C.; Deinhardt, *Virology* 90(2): 360-365; 1978.

e characteristics of the major virus glycoprotein (gp) of the nian sarcoma virus complex (SSV) were studied. The glycootein, designated gp70, was isolated in highly pure form m virus-free supernatants of tissue culture medium using munoadsorbents. SSV gp70 easily degraded to a ,000-dalton product designated gp45. Both gp preparations peared to be serologically and immunologically homogene- s. Antiserum prepared in rabbits to the purified SSV gp70 d a high neutralizing titer against SSV and was strongly totoxic for SSV-producing cells. The serum seemed to react ainly in a type-specific fashion with minor amounts of oup and no interspecies reactivities. The interspecies reacity of gp45 was somewhat reduced in comparison with 70. (14 refs)

8-6937 **Activation of Endogenous Type C Virus in BALB/c Mouse Cells by Herpesvirus DNA Oncornavirus Activation/Transfection).** (Eng) Boyd, A. L. Viral Oncology Program, Frederick Cancer Res. Center, rederick, MD, 21501); Derge, J. G.; Hampar, B. *Proc Natl cad Sci USA* 75(9): 4558-4562; 1978.

veral virion and nonvirion DNA's were tested for their ility to activate endogenous C-type virus in ALB/c-derived mouse cells using the calcium precipitation chnique. The DNA's from all herpesviruses (HV's) tested tivated xenotropic C-type virus synthesis, whereas under e same conditions the DNA's from vaccinia virus and simi- virus 40 were negative. Activation of C-type virus by HV NA's was essentially linear up to about 0.2 μg DNA, but decrease was usually observed at DNA concentrations ≥ 1 g. Activation was also observed with UV-irradiated HV's, t not with irradiated vaccinia virus. Activation of C-type rus by DNA from herpes simplex virus (HSV) was observed ter shearing or sonication of the DNA to an av size of $\times 10^6$ daltons, but it was not observed with DNA sonicated an av size of 1×10^6 daltons. Alkali denaturation of DNA m HSV or treatment of the DNA with DNase, but not Nase, destroyed its ability to activate C-type virus, as did osslinking of the DNA with 4,5′,8-trimethylpsoralen and ght. The results suggest that HSV may function as a cocarnogen. (20 refs)

78-6938 **Physical Mapping of Herpes Simplex Virus-induced Polypeptides.** (Eng) Marsden, H. S. (MRC Virology Unit, Inst. Virology, Univ. Glasglow, Glasgow G11 5JR, Scotland); Stow, N. D.; Preston, V. G.; Timbury, M.C.; Wilkie, N. M. *J Virol* 28(2): 624-642; 1978.

Correlation of the types of polypeptides induced by 29 herpes simplex virus type 1/type 2 intertypic recombinants with the crossover points in the recombinant DNAs enabled the map positions of many polypeptides to be deduced. The location on the physical map of 25 ^{35}S-methionine-labeled polypeptides, 11 phosphorylated polypeptides, and 4 glycosylated polypeptides was identified. Together with data from a previous study on the mapping of five immediate-early polypeptides, the results show that representatives of four groups of protein-immediate-early, late, phosphorylated, and glycosylated--map in both long and short regions. The functional organization of the herpes simplex virus genome does not therefore restrict any of these four groups to either the long or the short region. (19 refs)

78-6939 **Antibodies to Herpes Simplex Virus in Cervical Cancer.** (Jpn) Ishiguro, T. (Dept. Obstetrics and Gynecology, Kansai Medical Univ., Moriguchi-shi, Osaka Prefecture 570, Japan); Ozaki, Y. *Adv Obstet Gynecol (Jpn)* 30(1): 9-13; 1978.

Levels of antibodies to herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) were measured in 79 Japanese patients with cervical cancer, 11 with dysplasia, and 155 controls (including 145 healthy women and 10 with ovarian cancer). There was no significant difference in mean antibody titers among these groups. Furthermore, 18.2% of the dysplasia patients, 16.7% of those with carcinoma in situ (CIS), 11.1% of those with early invasive cancer (EIC), 3.2% of those with invasive cancer (IC), 0% of those with advanced cancer (AC), and 8.3% of healthy controls had no antibodies to either virus. Statistically, these data were not significant (SNS). The prevalence of single infection with HSV-1, as defined by an HSV-2/HSV-1 ratio of ≤ 65, was 36.4% in dysplasia, 50.0% in CIS, 27.8% in EIC, 19.4% in IC, 27.8% in AC, and 31.7% in healthy controls (data SNS). The prevalence of HSV-2-positive women, as defined by an HSV-2/HSV-1 ratio of ≥ 93, was 9.1% in dysplasia, 0% in CIS, 16.7% in EIC, 11.1% in AC, and 9.0% in healthy controls (data SNS); however, the prevalence in IC was 19.4%, a rate significantly higher than that in healthy controls ($p < 0.05$). These results suggest that HSV-1 is not associated with cervical cancer or dysplasia and that HSV-2 is involved with the progression but probably not the initiation of cervical cancer. (13 refs)

78-6940 **Preliminary Studies of a Non-Virionic Antigen Associated with Herpes Simplex Virus 1 and 2 (HSV_1-HSV_2).** (Eng) Accinni, R. (Clinica Medica II dell'Universita di Milano, Milano, Italy); Ferrara, R.;

Tarro, G.; Sisillo, E.; Privitera, L.; Biancardi, C.; Bartorelli, A. *In: Third International Symposium on the Detection and Prevention of Cancer held by the International Study Group for the Prevention and Detection of Cancer in New York, April 26-May 1, 1976.* International Study Group for the Prevention and Detection of Cancer (New York, NY): Vol. 1(part 1): 1193 pp.; 199-210; 1977.

Nonvirion antigens of herpes virus (HSV_1) were studied radioimmunologically, by gel filtration on Sephadex G-200, and by polyacrylamide gel electrophoresis (PAGE). In the radioimmunological study, soluble extracts of normal or infected cells incubated with pathological sera were found to possess different immunological properties. Gel filtration demonstrated two peaks in pellet extracts from infected cells that were absent in analogous extracts from normal cell pellets. PAGE demonstrated that soluble extracts from suspensions of infected cells contained three radioactive bands that were absent in extracts from normal cells. (7 refs)

78-6941 **Ultraviolet Reactivation of Herpes Simplex Virus Is Mutagenic and Inducible in Mammalian Cells.** (Eng) Bandyopadhyay DasGupta, U. (Dept. Therapeutic Radiology, Yale Univ. Sch. Medicine, 333 Cedar St., New Haven, CT, 06510); Summers, W. C. *Proc Natl Acad Sci USA* 75(5): 2378-2381; 1978.

Experiments were performed using the thymidine kinase (TK) locus of herpes simplex virus type 1 (HSV-1), strain Cl 101, to determine whether UV reactivation (Weigle reactivation) in mammalian cells is error-prone, thus leading to increased mutagenesis. The survival of UV-irradiated HSV-1 on UV-irradiated Vero cells was higher than that on unirradiated cells. A time lapse of 17 hr between irradiation of the host cells and infection with virus was needed to achieve max reactivation. In parallel experiments in which the frequencies of occurrence of the forward mutation in the TK gene of the virus were measured, growth of HSV-1 on UV-irradiated cells yielded progeny virus that had higher frequencies of TK- mutants than did progeny from infections of control cells. The time course of development of this mutagenic effect was the same as that for the development of UV-reactivation capacity. Furthermore, development of UV reactivation could be blocked by inhibition of protein synthesis. These findings suggest that an error-prone inducible UV-reactivation phenomenon exists in mammalian cells. (19 refs)

78-6942 **Studies on the Synthesis and Structure of Herpes Simplex Virus RNA.** (Eng) Stringer, J. R. (Univ. California, Irvine, Irvine, CA). *Diss Abstr Int [B]* 39(2): 511; 1978. (no refs)

78-6943 **Temperature-sensitive Mutants of Herpes Simplex Virus Type 1. Defective in Transcriptional and Post-transcriptional Functions Required for Viral DNA Studies.** (Eng) Parris, D. S. (Dept. Microbiology, Univ. Tennessee, Knoxville, TN, 37196); Courtney, R. J.; Schaffer, P. A. *Virology* 90(2): 177-186; 1978.

DNA- temperature-sensitive (*ts*) mutants of herpes simplex virus (HSV) representing four complementation groups (A, B, C, and D) were examined in temperature shiftdown experiments to determine whether viral DNA synthesis is inhibited at the level of transcription or translation at the nonpermissive temperature. Synthesis of viral DNA after temperature shiftdown appeared to require de novo transcription in the case of the *ts* A mutants, *ts* B2, and *ts* C4, but not in the case of *ts* D9. For *ts* B2 and *ts* C4, approx 2 hr was required for recovery of DNA synthesis capabilities following shiftdown. Viral transcripts specifying proteins required for DNA synthesis were synthesized 2 hr postinfection in *ts* D9-infected cells at the nonpermissive temperature. Polypeptide synthesis by all four mutants following shiftdown in the presence of an inhibitor was similar to that observed in mutant-infected cells maintained at the nonpermissive temperature in the absence of an inhibitor. Restoration of the wild-type pattern of viral polypeptide synthesis following shiftdown in the presence of an inhibitor was greater for the groups A, C, and D mutants than from the group B mutants. (14 refs)

78-6944 **Transformation of Hamster Embryo Fibroblasts by a Specific Fragment of the Herpes Simplex Virus Genome.** (Eng) Camacho, A. (Dept. Microbiology, Univ. Chicago, Chicago, IL, 60637); Spear, P. G. *Cell* 15(3): 993-1002; 1978.

Isolated restriction endonuclease fragments of the herpes simplex virus type 1 (HSV-1) genome were introduced into hamster embryo cells to identify DNA sequences capable of transforming the cells with respect to acquisition of properties correlated with tumorigenicity. One of the fragments generated by cleavage of HSV-1 DNA with the restriction endonuclease *XbaI* induced transformation at a frequency of about 10 colonies per quantity of fragment recovered from 1 μg of uncut DNA; fractions containing the other *Xba* fragments failed to induce transformation reproducibly, although occasional colonies were detected. The fragment with transforming activity (*XbaI*-F) is 15.5×10^6 daltons in mol wt and is located between 0.30 and 0.45 map units on the HSV-1 genome. The *XbaI*-F transformants were selected for their ability to replicate in low concentrations of serum; in addition, they were found to attain high saturation densities in the presence of 10% serum and to form colonies in semisolid medium. Moreover, the transformed cells produced at least one viral gene product (a membrane glycoprotein) encoded in the fragment used for transformation, indicating not only that viral DNA was incorporated in the cells but that viral genes were expressed. (37 refs)

6945 **Genital Herpesvirus in the Etiology of Human Cervix Uteri Cancer.** (Eng) Kessler, I. I. (Dept. demiology, Johns Hopkins Univ., Baltimore, MD, 05). *In: Third International Symposium on the Detection Prevention of Cancer held by the International Study up for the Prevention and Detection of Cancer in New k, April 26-May 1, 1976.* International Study Group for Prevention and Detection of Cancer (New York, NY): 1(part 1): 1193 pp.; 211-229; 1977.

o investigations of the possible role of herpesviruses in vical cancer (CC) were made. The first was a retrospective, e-control study of 350 Yugoslavian women with histologi- y confirmed squamous carcinoma of the uterine cervix 350 matched controls. Herpes simplex virus type 2 V-2) antibody titers were higher among the CC patients n the controls. The relative risk of CC in women positive HSV-2 was significantly increased, even after adjustments e made for the effects of 34 epidemiologic factors associat- with CC. In addition, compared with controls, women o developed CC were more likely to smoke and drink al- olic beverages, they had higher blood pressures, their par- s tended to be older at their birth, they had more multiple rriages and an earlier start of sexual activity, consistently uced coital frequency, and they were more likely to have mal menstrual histories. There was an unexpected two- hreefold greater mortality, especially at younger ages, of first husbands of the CC patients, compared with the trol first husbands. In a second study, still in progress, o large groups of women are being observed: one married men who, at some other time, had wives who developed and a second married to men without such histories. To e, abnormal pap tests have been found in 13.6% of the se" wives vs 7.2% of the control wives. CC or carcinoma itu has been diagnosed in 3.5% of the case wives and 1.2% he control wives. These data support an etiological role HSV-2 in CC and they suggest that hormonal factors may o be involved. (23 refs)

-6946 **Evaluation of the Effects of Phosphonoacetic Acid and 2-Deoxy-D-glucose on *Herpesvirus miri* and Epstein-Barr Virus.** (Eng) Ablashi, D. CI-Frederick Cancer Res. Center, Fort Detrick, Frede- k, MD, 21501); Armstrong, G.; Fellows, C.; Easton, J.; arson, G.; Twardzik, D. *In: Third International Symposi- on the Detection and Prevention of Cancer held by the ternational Study Group for the Prevention and Detection Cancer in New York, April 26-May 1, 1976.* International dy Group for the Prevention and Detection of Cancer ew York, NY): Vol. 1(part 1): 1193 pp.; 245-261; 1977.

e effect of phosphonoacetic acid (PAA) and leoxy-D-glucose on *Herpesvirus saimiri* (HVS) and on Ep- in-Barr virus (EBV) was studied in vitro. PAA significant- and reversibly inhibited the replication of HVS in African een monkey kidney (Vero) cells when it was added immedi- ately after a 2-hr absorption period, but not later. The compound had no effect on the virus itself, on viral absorption, or on the induction of early antigen, but it did inhibit the production of late and membrane antigens almost completely. The failure of more template to reverse the inhibition of Vero cell DNA polymerases by PAA suggests that PAA does not interact with the uncoated DNA of input HVS in Vero cells. Rather, PAA may block a cellular process essential for HVS replication. PAA had no effect on the induction of endogenous or exogenous EBV early antigen, and it did not inhibit the appearance of EBV nuclear antigen in actively replicating Raji cells. Thus, the compound may have no effect on the replication of EBV DNA in Raji cells. This DNA is either integrated with the cell genome or in a free circular form. However, under certain conditions, PAA inhibited the expression of EBV membrane and viral capsid antigens. If the resistance of HVS to PAA, beginning 2 hr after the end of absorption, is similar to that of EBV DNA in Raji cells, infecting HVS DNA may assume a relatively stable and resistant form within the infected cell. It is not known if this would involve integration of input HVS DNA with the cellular genome. 2-Deoxy-D-glucose had no effect on HSV. (30 refs)

78-6947 **Host Cell Reactivation of Epstein-Barr Virus in Normal and Repair-defective Leukocytes.** (Eng) Henderson, E. E. (Dept. Microbiology and Immunology, Temple Univ. Sch. Medicine, Philadelphia, PA, 19140). *Cancer Res* 38(10): 3256-3263; 1978.

Epstein-Barr virus (EBV)-induced transformation efficiencies were quantitated for peripheral blood WBC from two patients with xeroderma pigmentosum (XP) and a patient with Cockayne's syndrome. No differences in transformation efficiencies were observed among XP, Cockayne's syndrome, or normal adult WBC, as judged by transformed centers or limiting dilution assays. However, when either the WBC or the infecting EBV was UV-irradiated prior to virus exposure, XP WBC showed a greater decrease in ability to undergo in vitro transformation. The doses of the transforming functions of the B95-8 strain of EBV lethal to 37% of the animals were 70, 725, and 750 ergs/mm^2 when measured in XP, XP heterozygotic, and normal adult WBC, respectively. Transforming activity of UV-irradiated EBV could be partially restored by illuminating infected XP WBC with visible light 36 hr after virus exposure. Illumination with visible light had little effect on transformation of neonatal or normal adult WBC by UV-irradiated EBV. Colony formation in soft agarose by the resulting lymphoblastoid cell lines established from primary XP or Cockayne's syndrome WBC showed increased sensitivity to UV irradiation when compared with lymphoblastoid cell lines established from heterozygotic or normal individuals. These results indicate that EBV is similar to other herpesviruses in being subject to host cell reactivation and that the EBV-induced transformation does not require or alter these functions. (39 refs.)

78-6948 **Detection of Epstein-Barr Virus in Biopsied Malignant Lymphoma Cell and Its Continuous Culture.** (Eng) Suzuki, T. (First Dept. Pathology, Niigata Univ. Sch. Medicine, 1-Bancho, Asahimachi-dori, Niigata 951, Japan); Oboshi, S.; Ishihara, N.; Emura, I.; Ohnishi, Y.; Sairenji, T.; Hinuma, Y. *Gann* 69(2): 213-221; 1978.

The detection of the Epstein-Barr (EB) virus genome in the tumor cells from a patient with non-Burkitt-type B-cell lymphoma and the establishment of tumor cell lines (Fujimaki-I and/-II) from these cells are described. More than 80% of the tumor cells obtained from a pericardial effusion of the patient were positive for EB nuclear antigen (EBNA), and herpes-type virus particles were detected in the tumor cell nuclei. Tumor cells from a biopsy specimen of the original sc tumor grew continuously in vitro without any cell death (Fujimaki-I) and tumor cells from the pericardial effusion proliferated without a growth lag phase or cell death (Fujimaki-II). The cytological characteristics of the Fujimaki-II cells were similar to those of the tumor cells in vivo. Seventy percent of these cells were positive for EBNA and 4% were positive for EB virus capsid antigen. The modal chromosome number of the cells in the twenty-fourth generation was 46, and no marker chromosomes were found. IgG was monoclonally demonstrated in the culture medium. Fatal generalized toxoplasmosis resulted when the original tumor tissue was inoculated ip, sc, or under the renal capsule in athymic nude mice. Fujimaki-II cells heterotransplanted sc or ip into mice did not induce tumors, and the virus released by these cells did not transform cord blood lymphocytes. These data suggest that the Fujimaki cells did not produce detectable amounts of infectious virus. This may be the first case of non-Burkitt type lymphoma in which the EB virus genome was directly detected in the tumor cells. (22 refs)

78-6949 **A Study on Epstein Barr Virus Receptor Activity in Cell Free Extracts of Human Lymphoblastoid Cells.** (Eng) Ng, M. H. (Dept. Microbiology, Queen Mary Hosp. Compound, Univ. Hong Kong, Hong Kong, China); Lui, S. W.; Chan, K. H. *Arch Virol* 58(3): 221-233; 1978.

The detection of Epstein Barr virus (EBV) receptor activity in the surface extract of Raji cells and to a lesser extent in that of BJAB cells both are B lymphoblastoid cells susceptible to EBV infection) is reported, and results of a preliminary attempt to purify the Raji cell receptors are also presented. Receptor activity was not detected in extracts of P_3HR-1 cells and human diploid fibroblasts, neither of which are known to be susceptible to EBV infection. Receptor activity in the Raji cell extract was found to be associated with membranous structures, which may have rendered the activity resistant to treatment with trypsin and sonication. The receptor activity was abrogated if the extract was exposed to neutral detergent. Binding of receptor activity was observed when Raji cell extract was chromatographed on a column of immobilized EBV components. Subsequent electrophoretic analysis showe however, that this procedure did not result in an appreciat purification of the receptor activity. Neutral detergent-trea ed extract was similarly chromatographed. The resulting el ates did not contain detectable receptor activity but were le heterogeneous in protein content compared with the origin extract. It is uncertain if these EBV binding proteins are i volved in the receptor activity of the extract. (17 refs)

78-6950 **Expression of Altered Ribonucleotide Redu tase Activity Associated with the Replication the Epstein-Barr Virus.** (Eng) Henry, B. E. (Dept. Microl ology, Univ. Mississippi Medical Center, Jackson, M 39216); Glaser, R.; Hewetson, J.; O'Callaghan, D. J. *Virolo* 89(1): 262-271; 1978.

Extracts of control and 5-iododeoxyuridine (IUdR)-induc epithelial/Burkitt hybrid cells (D98/HR-1) and Raji ce were assayed for ribonucleotide reductase (RR) activity in t presence and absence of hydroxyurea (HU). The expressi of the Epstein-Barr virus (EBV) genome in these cells can regulated by induction with IUdR or superinfection with t virus. HU inhibited the enzyme activity of contr D98/HR-1 and Raji cells by $>70\%$ at both low (2×10^{-4}M and high (5×10^{-4}M) concentrations. However the reducta activities of IUdR-induced D98/HR-1 cells, Raji cells supe infected with EBV, and IUdR-induced Raji cells were resis ant to both levels of HU; enzyme activities of 85% to >100 of control values were obtained in all cases. Under conditio that allowed only partial expression of the EBV genome (b fore removal of IUdR; early time after superinfection), si nificant levels (70%-85%) of HU-resistant RR activity we obtained in the presence of 2×10^{-4}M HU, but only 30%-45 of control reductase activity was observed at the higher co centration. Mixing experiments employing combinations various D98/HR-1 control and induced cell extracts indica ed that the HU-resistant reductase activity of induc D98/HR-1 cells was due to altered enzyme activity and n to nonenzymatic factors. Experiments in which HU w preincubated with control and induced cell extracts show that the HU-resistant RR in extracts of induced D98/HR cells was not due to inactivation of the inhibitor by an enzyn or factor present in these cells. These findings, together wi similar findings for equine herpesvirus type 1 and herpes sin plex virus types 1 and 2, suggest that alteration of RR activi may be a key event in herpesvirus replication. (22 refs.)

78-6951 **Epidemiological Evidence for Causal Relatio ship Between Epstein-Barr Virus and Burkitt Lymphoma from Ugandan Prospective Study.** (Eng) de-Th G. (International Agency Res. Cancer, WHO, 150 cours A bert Thomas, 69372 Lyon, France); Geser, A.; Day, N. E Tukei, P. M.; Williams, E. H.; Beri, D. P.; Smith, P. G

A. G.; Bornkamm, G. W.; Feorino, P.; Henle, W. *Na-* 74(5673): 756-761; 1978.

g 1972-1977, a large, prospective, seroepidemiological was undertaken in Uganda to evaluate evidence that n-Barr virus (EBV) is a necessary factor for the devel- it of Burkitt's lymphoma (BL). From 1972 to 1974, samples were taken from 42,000 children up to age 8. 77, 31 cases of BL had been diagnosed in the area, 14 ch were in children originally bled. (Only 3/31 patients nissed at original bleeding; the rest were from a region vered by the field team or were too old for inclusion.) 14 children, the interval between initial serum collec- nd BL onset was 7-54 mo. Significantly higher titers ibodies (ab's) to virus capsid antigen (VCA) were seen -BL sera than in matched controls. These titers were indicating that the high ab levels associated with BL resent long before clinical onset. There were no marked nces in pre- and post-BL ab titers to herpes simplex and cytomegalovirus, eliminating the possibility that as due to a long-standing defect in cell-mediated im- y. Six of seven patients with detectable EBV DNA in tissue had prediagnosis VCA ab titers high or higher hose in controls. Thus, the association of BL with pre- e VCA titers may be confined to cases characterized V DNA in the tumor cells. There may be two types with different etiologies, one associated with EBV and predominantly in tropical areas and one not associated BV and found in temperate areas. The results strongly rt a causal association between EBV infection and BL. ver, even in a region where infection with EBV is nearly tous, only 1 child in 1,000 develops BL; therefore, oth- ctors are required. The potential oncogenicity of EBV e realized only in exceptional circumstances. (45 refs.)

952 **A New Manifestation of Infection with Epstein-Barr Virus.** (Eng) Smith, H. (Dept. Infec- Diseases and Immunological Medicine, Northwick Hosp., Harrow HA1 3UJ, England); Denman, A. M. *ed J* 2(6132): 248; 1978.

yr-old woman with a specific T-lymphocyte defect suf- a prolonged bizarre illness produced by Epstein-Barr EBV). The illness was intermediate in severity and out- between the common self-limiting infectious mononu- and the more aggressive malignant condition associat- th this virus. Antibodies to EB virus capsid antigen ect immunofluorescence) showed a progressive rise in It is suggested that the patient suffered from a specific in cell-mediated immunity to EBV, shown morpholog- in her failure to produce atypical mononuclear cells and functionally in her inability to mount a specific reac- gainst cells infected by this agent. The patient's history ere varicella indicated that there was a constitutional ty to react to DNA containing herpesviruses. The pa- esponded to treatment with corticosteroids. (4 refs)

78-6953 **Study of Epstein-Barr Virus-determined Nuclear Antigen (EBNA) by Chromatography on Fixed Cell Nuclei.** (Eng) Hirsch, I. (Dept. Experimental Virology, Inst. Sera and Vaccines, 101 03 Prague, Czechoslovakia); Suchankova, A.; Zavadova, H.; Vonka, V. *Int J Cancer* 22(5): 535-541; 1978.

A low concentraton of NaCl (50 mM) and pH 6.0 were found to be optimal conditions for the in vitro conversion of Epstein-Barr virus nuclear antigen (EBNA)-negative nuclei to EBNA-positive forms by the addition of complement-fixing (CF) antigen from the Raji human lymphoblastoid cell lines. The conversion was sensitive to treatment with DNase but not RNase, which suggests that EBV-CF antigen binds specifically to nuclear DNA. Identical conditions were optimal for both the elution of EBNA from in vitro-converted nuclei and the adsorption and elution of EBV-CF antigen in DNA-cellulose chromatography. This indicates that the DNA-binding properties of EBNA antigen can be studied in a microchromatographic system employing fixed nuclei. The advantages of this method are its simplicity, capacity for analyzing many samples per experiment, and requirements of very small amounts of material. Elution patterns for EBNA were signficantly different when nuclei from different cell lines (Raji, Ramos, and P3HR-1) were converted to EBNA positivity. EBNA was eluted from converted nuclei of EBV genome-positive P3HR-1 cells at an almost 0.1 M higher concentration of NaCl than was necessary for a similar degree of elution from nuclei of EBV genome-negative Ramos cells. (22 refs)

78-6954 **DNA of Epstein-Barr Virus. IV. Linkage Map of Restriction Enzyme Fragments of the B95-8 and W91 Strains of Epstein-Barr Virus.** (Eng) Given, D. (Dept. Medicine, Univ. Chicago, Chicago, IL, 60637); Kieff, E. *J Virol* 28(2): 524-542; 1978.

The arrangement of restriction enzyme sites *Eco*RI, *Hsu* I, and *Sal* I in the DNA of the B95-8 and W91 isolates of Epstein-Barr virus (EBV) was determined from the size of the single-enzyme-cleaved fragments and from blot hybridizations that identify which fragments cut from the DNA with one enzyme contain nucleotide sequences in common with fragments cut from the DNA with a second enzyme. The data indicate that there is a consistent and unique sequence arrangement of approx 95 to 100 x 10^6 daltons of B95-8 strain EBV DNA. Both termini were variable in length, but the opposite ends of the molecule contained homologous sequences. The high degree of homology between the opposite ends of the molecule and the similarity in size of the "additional" 500-base pair segments suggest that there are identical repeating units at both ends of the DNA. The size of almost all *Eco*RI, *Hsu* I, and *Sal* I fragments of W91 DNA was identical to that of the B95-8 DNA fragments except that W91 DNA contained approx 7 x 10^6 daltons of "extra" DNA in the *Hsu* I-D-*Eco*RI-C overlap region of B95-8 DNA. Furthermore, the restriction endonuclease fragments of the W91

and B95-8 DNA's, which are of similar mol wt, had homologous nucleotide sequences. Morever, the W91 fragments contained only sequences from a single region of the B95-8 genome. Two lines of evidence indicate that the extra DNA in W91 *Eco*RI C and *Hsu* I D_1 and D_2 fragments is viral DNA and not cellular. (48 refs)

78-6955 **Electron Microscopic Studies of Tumor Viruses. II. Entry and Uncoating of Epstein-Barr Virus.** (Eng) Miyamoto, K. (Pathology Div., Natl. Cancer Center Res. Inst., Tsukiji 5-1-1, Chuo-ku, Tokyo 104, Japan); Sairenji, T.; Hinuma, Y. *Microbiol Immunol* 22(8): 463-474; 1978.

The entry of Epstein-Barr virus into human lymphoblastoid cells (Daudi) was studied ultrastructurally. Two types of virions were observed on the cell surface: the zone separating the capsid from the dense core in one case was electron-translucent, but this zone in the other case was more dense because of the presence of finely granular material. These virions were referred to as light and dense particles, respectively. Virus attached to the cell surface at time 0 consisted of 56% dense particles, 41% light particles, and 3% empty particles (ie, devoid of cores). In samples taken at time 0, no free virus was found in the cell cytoplasm, although a few ($< 1\%$) of the cells showed degenerative changes. When the cells were warmed to 37 C, two distinct types of interaction between the viral envelope and cell membrane ensued, these changes being observed most frequently in samples taken at 30-60 min. The first change was simultaneous dissolution of both the viral envelope and cell membrane at the point of attachment, presumably resulting in passage of viral capsids into the cytoplasm. The other change was dissolution only of the cell membrane at the site of attachment, resulting in penetration of the enveloped virus. Envelope dissolution appeared to occur subsequently in the cytoplasm, with release of capsids. Fusion of the viral envelope with the cell membrane was not observed. Enveloped viruses may differ in the mechanism by which they gain entry and in their ability to cause cell fusion at early stages of infection. (21 refs)

78-6956 **Acute Lymphocytic Leukemia in the Course of a Primary Herpes Infection with Hepatitis and Bone Marrow Aplasia in a Two-Year-Old Child.** (Fre) De Lumley, L. (Travail du Service de Pediatrie I, Centre Hospitalier Universitaire Dupuytren, 87000 Limoges, France); Malinvaud, G.; Boulesteix, J.; Gaillard, S.; Colombeau, M. C. *Pediatrie* 33(3): 291-298; 1978.

Acute lymphocytic leukemia (ALL) developed in a 2-yr-old boy admitted to the hospital with viral hepatitis. Prior to admission, the child was given sulfamethoxazole, trimethoprime, and pipebuzone for fever and stomatitis. Acute hepatitis was diagnosed on the basis of fever, icterus, pruritis, and hepatomegaly. Blood studies revealed anemia, leukopenia (10% polynuclear neutrophils, 90% lymphocytes), and thrombocytopenia. Viral serology was negative; however, there was a high level of antiherpes antibodies. The patient was treated with cefalotine, (125 mg/kg/day), gentamycin (4 mg/kg/day), prednisone (2 mg/kg/day), and RBC and WBC transfusions. The cefalotin was replaced by colistin (1 million units/day) when a dermatitis reaction occurred. The patient improved and was well enough to leave the hospital on the 31st day with regression of hepatic and inflammatory symptoms. Four months after the initial admission, he was readmitted with clinical symptoms of a tumor, including hepatosplenomegaly and widespread adenopathy. A bone marrow puncture revealed 82% small lymphoblasts. Despite treatment with combination chemotherapy for ALL, the child died 17 mo after the first admission. The question arises as to whether the herpesvirus infection was severe as a result of a preleukemic condition or whether the herpesvirus was responsible for the ALL. (26 refs)

78-6957 **Establishment of a Human Hepatoma Cell Line Which Produces Hepatitis B Surface Antigen (HBsAg).** (Eng) Alexander, J. (Virus Cancer Res. Unit., Poliomyelitis Res. Foundation, Johannesburg, South Africa); Bey, E.; Macnab, G. *In: Third International Symposium on the Detection and Prevention of Cancer held by the International Study Group for the Prevention and Detection of Cancer in New York, April 26-May 1, 1976.* International Study Group for the Prevention and Detection of Cancer (New York, NY): Vol. 1(part 1): 1193 pp.; 321-330; 1977.

Biochemical and immunological studies were made of a cell line established from a primary liver carcinoma of a 24-yr-old man. One aim of the studies was to examine the cells for the presence of virus particles and viral antigens. The cells, which had been in continuous culture for 30 mo, had a male human chromosome pattern. The modal chromosome number was 56.6, and markers were present. The enzymes conformed to the human pattern, and glucose-6-phosphate dehydrogenase type A isozyme was found. Electron microscope studies showed that the cells contained glycogen granules and that microvilli and smooth endoplasmic reticulum were common. There was no evidence of virus particles, and there were no signs of lesions commonly associated with hepatitis-infected liver cells. The cells produced hepatitis B surface antigen (HBsAg), which was detected predominantly in the culture supernatant. The antigen levels increased with time, and antigen was produced at approx 500 $\mu g/day/10^6$ cells. HBsAg activity in the culture supernatant was associated with amorphous particles ranging from 16 to 24 nanometers in diameter. The particles had a buoyant density in CsCl of 1.18-1.2 g/cm^3. (23 refs)

78-6958 **Hepatocellular Carcinoma Associated with HBs Antigen: A Study of 25 Cases from Vietnam.** (Fre) Doury, J. C. (Laboratoire d'anatomie pathologique, In-

t de Medecine tropicale du service de sante des armees, du Pharo, 13998 Marseille-Armees, France); Roche, J. Brisou, B. *Rev Epidemiol Sante Publique* 26(2): 161-170; 3.

g orcein staining and indirect immunofluorescence on ffin sections, hepatitis B surface antigen was demonstrat- 64% of 25 hepatocellular carcinomas (including 1 bone stasis) in Vietnamese patients. Literature findings sug- ing a causal role for hepatitis B virus in primary cancer are discussed. (29 refs)

5959 **A Virus Similar to Human Hepatitis B Virus Associated with Hepatitis and Hepatoma in dchucks.** (Eng) Summers, J. (Inst. Cancer Res., Fox se Cancer Center, Philadelphia, PA, 19111); Smolec, J. Snyder, R. *Proc Natl Acad Sci USA* 75(9): 4533-4537; .

lence indicates that human hepatitis B virus (HBV) be- s to a novel class of DNA viruses that may be causative ts of hepatitis in species other than humans. Approx of the serum samples from woodchucks at a research ratory contained DNA polymerase (Pase)-containing cles in amounts comparable to those found in hepatitis rface antigen (HBsAg)-positive sera. Three animals 307, CW326, and CW316) subsequently died and were ed further to determine the possible relationship between particles and hepatic lesions. CW307 and CW326 had tocellular carcinomas and evidence of chronic active titis, and their sera contained detectable levels of endoge- DNA Pase, but serum from CW316, with no apparent tic lesions, had no detectable DNA Pase-containing par- s. Large numbers of spherical and tubular forms approx anometers (nm) in diameter were found in the serum of 307 and CW326. They strongly resembled HBsAg, but ed at a slightly lower density in CsCl gradients. A second of particles banding at 1.215 g/cm^3 contained a DNA DNA Pase activity. The DNA was similar in size and cture to HBV DNA. In addition, each DNA molecule ared to contain a substantial single-stranded region, as HBV DNA. The action of the internal DNA Pase on ingle-stranded region accounts for the endogenous DNA activity observed in the serum of some woodchucks. lly, fractions of the CsCl gradient that had endogenous A Pase activity contained double-layered particles, 55 nm ameter, that resembled Dane particles, thought to be the plete virus of hepatitis B. It is likely that these double-lay- particles contain the DNA and DNA Pase activity. The like particles found in the diseased woodchucks were ar but not identical to those associated with hepatitis B. minary experiments indicate that the exposed antigenic on the small particles do not cross-react with HBsAg. efs)

5960 **An Electroncytochemical Study of 5′-Nucleotide Phosphodiesterase in Hepatoma, Cirrhosis and Hepatitis.** (Eng) Tsou, K. C. (Harrison Dept. Surgical Res., Sch. Medicine, Univ. Pennsylvania, Philadelphia, PA, 19104); Lo, K. W.; Rhoads, J. E.; Mackie, J. A. *In: Third International Symposium on the Detection and Prevention of Cancer held by the International Study Group for the Prevention and Detection of Cancer in New York, April 26-May 1, 1976.* International Study Group for the Prevention and Detection of Cancer (New York, NY): Vol. 1(part 1): 1193 pp.; 331-342; 1977.

Polyacrylamide gel electrophoresis analyses have recently shown that there is an isozyme of 5′-nucleotide phosphodiesterase (5′-NPDase) in the sera of patients with hepatitis B and hepatoma and in some with cirrhosis. To determine the significance of this enzyme in linking the etiology of hepatoma with hepatitis B-related virus, hepatoma tissues from two patients were studied ultrastructurally and electron cytochemically. The sera of these two patients were positive for 5′-NPDase and negative for hepatitis B surface antigen (HBsAg). α-Fetoprotein levels were 10 and 400 nanograms/ml, respectively. Both tumor samples were positive for viruslike particles resembling Dane particles of hepatitis B serum. These particles were also seen in cirrhotic areas of the liver, but most were found enclosed in cytoplasmic vesicles. One interesting feature of the cytoplasmic organelles was an abundance of circular vesicular membranes that often surrounded the mitochondria. This feature was also seen in the cirrhotic areas of both patients. An electron cytochemical method demonstrated the presence of deposits of 5′-NPDase activity on particles obtained by precipitation of hepatitis B serum with anti-HBsAg. These data suggest that there may be a group of human hepatomas etiologically linked to hepatitis B-associated virus and that some cases of cirrhosis may be a reflection of the host-immune response to viral proliferation. A possible role for 5′-NPDase in hepatitis B infection is suggested. (48 refs)

78-6961 **Liver Cell Dysplasia and Hepatitis B Surface and Core Antigens in Cirrhosis and Hepatocellular Carcinoma of Autopsy Cases.** (Eng) Sakurai, M. (1st Dept. Pathology, Osaka Univ. Medical Sch., Osaka, Japan). *Acta Pathol Jpn* 28(5): 705-719; 1978.

The relationships between cirrhosis, hepatoma, liver cell dysplasia, serum and cellular levels of hepatitis B surface and core antigens (HBsAg and HBcAg), and serum levels of antibody to HBsAg (anti-HBs) were studied based on examination of tissues from 180 autopsy cases with cirrhosis and/or hepatoma. Dysplasia was not associated with hepatoma in the absence of cirrhosis and was significantly more common in cirrhotic livers with tumors than in cirrhotic livers without tumors. The association between cirrhosis and dysplasia did not vary with age or sex. There was a significant correlation between high HBsAg levels and cirrhosis plus dysplasia, and orcein-positive cells were found significantly more often in cirrhotic livers than in noncirrhotic livers. The morphological characteristics of the orcein-positive liver cells could not

be correlated with dysplasia or hepatoma. HBcAg levels did not correlate significantly with dysplasia or hepatoma, but they did correlate with active cirrhosis, marked liver cell degeneration and necrosis, and membranous diffuse-type HBsAg in liver cells. (21 refs)

78-6962 **Detection of Adenovirus Integration Sites in Host Cell Chromosomes.** (Eng) McDougall, J. K. (Cold Spring Harbor Lab., Cold Spring Harbor, NY, 11524); Dunn, A. R.; Gallimore, P. H. *In: Third International Symposium on the Detection and Prevention of Cancer held by the International Study Group for the Prevention and Detection of Cancer in New York, April 26-May 1, 1976.* International Study Group for the Prevention and Detection of Cancer (New York, NY): Vol. 1(part 1): 1193 pp.; 129-137; 1977.

The location and function of integrated adenovirus (Ad) DNA sequences in rodent and human cells were determined by several approaches. Somatic cell hybrids were derived by fusion of virus-transformed rat cells and mouse cells deficient in thymidine kinase. The hybrid lines were isolated by a double selective system. Chromosomes (Chr) in the hybrids bearing mouse centromeres were identified by in situ hybridization with mouse satellite complementary RNA as the probe. The only rat Chr positively identified in the hybrid lines were 1, 2, 11, 12, 17, and 19; however, none of these Chr was consistently present in every hybrid line. All hybrids were screened for virus messenger RNA (mRNA) by in situ hybridization using ^{125}I-labeled Ad DNA. None of the six rat Chr identified was consistently present in viral mRNA or T-antigen-positive lines, and none of the 15 rat isozymes tested, apart from thymidine kinase, was always present in hybrid cells expressing viral functions. Thus, cytogenetic analysis and rat isozyme segregation data indicated that many hybrids contained new Chr translocations not present in the parental lines and that none of the marker Chr in the transformed cells appeared in the hybrid lines. The situation with an Ad-transformed human cell line was similar, in that these cells were heterogeneous in Chr constitution, with an av count in the triploid range and with only a small amount of viral DNA/diploid quantity of human DNA. Thus, Ad DNA is integrated into only a few Chr of rat cells, but it was not possible to define a specific Chr associated with the expression of Ad T antigen. (26 refs)

78-6963 **Synthesis of a Structural Adenovirus Polypeptide in the Absence of Viral DNA Replication.** (Eng) Persson, H. (Dept. Microbiology, Biomedical Center, Box 581, S-751 23 Uppsala, Sweden); Pettersson, U.; Mathews, M. B. *Virology* 90(1): 67-79; 1978.

The kinetics and control of adenovirus type 2 (Ad2) polypeptide IX (ppIX) synthesis were studied in HeLa cells pulse-labeled with ^{35}S-methionine at different times beginning at 2 hr postinfection. Cell extracts were immunoprecipitated with antisera against Ad2 early polypeptides or structura components, and the immunoprecipitates were analyzed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE). Polypeptide IX, a structural protein, was first detectable 6 hr postinfection, 4 hr before ppII and III, and 6 hr before ppIV, the major structural components. When cells were treated with cytosine arabinoside for 1 hr after Ad2 infection, ppIX antiserum precipitated a 12,000-mol-wt peptide that specifically comigrated with ppIX on SDS-Page thus demonstrating the synthesis of ppIX in the absence of viral RNA replication. Cycloheximide which blocks protein synthesis as well as viral replication, did not inhibit ppIX synthesis or accumulation of its messenger RNA (mRNA), although the mRNA's of the other structural components remained undetectable. RNA from cycloheximide-treated, virus-infected cells also directed the synthesis of a 12,000-mol-wt polypeptide that comigrated with ppIX and was precipitated by antiserum against ppIX. Size fraction of the RNA indicated that it sedimented at the same rate, 9S, as the late mRNA for ppIX. Because transcription of this polypeptide occurs at a different time and is under different regulation than the other late structural genes, ppIX may have functions in addition to its structural role in the virus particle. (48 refs)

78-6964 **The Spliced Structures of Adenovirus 2 Fiber Message and the Other Late mRNAs.** (Eng) Chow, L. T. (Cold Spring Harbor Lab., P.O. Box 100, Cold Spring Harbor, NY, 11524); Broker, T. R. *Cell* 15(2): 497-510; 1978.

Several rightward-transcribed (R)-strand transcripts in the adenovirus 2 (Ad2) map interval between coordinates 27 and 50 were mapped. In common with eight previously reported Ad2 messenger RNA's (mRNA's), four RNA species were identified with the same tripartite leader sequence derived from coordinates 16.6, 19.6, and 26.6. This leader was joined to messages with 5′ ends located at coordinates 29.1, 30.5, 33.9, and 42.8, respectively. The RNA transcripts extending from 29.1 to 39.0 covered most or all of the virus-associated RNA genes (29.0-30.1). The late RNA's could be grouped into several families of transcripts that differed substantially in the coordinate at which the leader sequences were attached to the main body of message. The number of RNA species transcribed from the Ad2 chromosome between coordinates 29 and 50 exceeded the number of identified Ad2 proteins. A subpopulation of the polysomal mRNA's for the fiber protein, the most distal gene (86.3-91.2) in the rightward transcription unit, had a fourth leader component "y" (78.6-79.1) in addition to the common tripartite leader sequences. Less frequent fiber RNA species had a fifth "x" (79.6-77.3) and/or sixth "z" (84.7-85.1) leader segment. mRNA transcribed at late times from the L strand between coordinates 15.0 and 11.0 had a single component leader located 200 bases from the main body of the gene (coordinates 16.1-15.7). This leader originated from a site close to the first leader component (16.5-16.6) of the R-strand messages. (38 refs)

-6965 **Enucleated Cells as an Approach to the Study of Cytoplasmic Events in Adenovirus Replica-n (Meeting Abstract).** (Eng) Gayathri, A. K. (Dept. Hu-n Genetics, Yale Univ., New Haven, CT); Hodge, L. D. *Cell Biol* 79(2, part 2): 402a; 1978. (no refs)

-6966 **A Supplementary Adenoviral Leader Sequence and its Role in Messenger Translation.** (Eng) nn, A. R. (Cold Spring Harbor Lab., P.O. Box 100, Cold ing Harbor, NY, 11524); Mathews, M. B.; Chow, L. T.; nbrook, J. *Cell* 15(2): 511-526; 1978.

e population of adenovirus 2-simian virus 40 (Ad2-SV40) rid messenger RNA's (mRNA's) generated late in the ction of HeLa cells with the Ad2-SV40 hybrid 2+ND1 dp2 was studied biochemically and by electron roscope heteroduplex analysis. During the course of lytic ction with the hybrid, a viral mRNA was synthesized ose 5′ end included the start of the Ad2 fiber gene and ose 3′ end lay in SV40 sequences. Two forms of this NA existed in the cytoplasm of HeLa cells at late times nfection. Both forms contained the conventional tripartite der present on "late" Ad2 mRNA's, but they differed in presence or absence of a fourth leader sequence consisting 180 nucleotides of AD2 sequences located 2,000 nucleo-s upstream from the gene. Both forms of the hybrid NA were isolated by fractionation of total poly(A)-con-ning Ad2+ND1 dp2 late cytoplasmic RNA in methyl rcuric hydroxide-agarose gels. It was established that the sence or absence of the fourth leader sequence had little no influence on the ability of the messenger to direct the thesis of the 23,000- to 24,000-dalton protein(s) in a l-free translation system derived from rabbit reticulocytes. refs)

-6967 **Activation of RNA Particles from Human Tumors by Human Adenovirus.** (Eng) Winters, W. (Univ. Texas Health Science Center, San Antonio, TX); ri, A.; Sykes, J. A.; O'Toole, C. *In: Third International mposium on the Detection and Prevention of Cancer held the International Study Group for the Prevention and De-tion of Cancer in New York, April 26-May 1, 1976.* Interna-nal Study Group for the Prevention and Detection of Can-(New York, NY): Vol. 1(part 1): 1193 pp.; 279-292; 1977.

ltures of various human tumor and normal cells were wn in standard medium and inoculated with 5-500 que-forming units/cell of stock adenovirus 5 (Ad5). Cells 15/20 sarcomas of different histologic types, 9/10 melano-s, and those of all breast, cervical, and squamous cell car-omas examined readily supported complete Ad5 replica-n. The cells contained membrane-enclosed particles, and culture supernatants contained RNA particles with spe-ic DNA polymerase activities. The normal embryonic, fet-newborn, and adult cells also supported Ad replication. Cell-free fluids of untreated or Ad-infected permissive human tumor and normal cell cultures had no DNA polymerase activities. Cell-free fluids of nonpermissive human tumor cells contained DNA polymerase activities at 3-9 days following Ad5 infection. The activation of detectable DNA polymerase-containing particles was dose- and time-dependent. Additional studies designed to label specifically the DNA and RNA in replicate cultures revealed that cell-free supernatants contained ^{3}H-uridine-labeled particles with densities of 1.14-1.18 g/ml in equilibrium sucrose density gradients. DNA polymerase activities were detected within this range of density in fractions taken from these gradients. Heat-inactivated and antiserum-neutralized Ad5 did not infect or activate human tumor cells. The results suggest that infectious viruses with which humans normally have contact could, under proper host conditions, play a role in activating latent viruses associated with human tumors. (23 refs)

78-6968 **Defective Virions of Simian Adenovirus 7 Produced by One Passage at High Multiplicity of Infection.** (Eng) Price, J. A. (Dept. Microbiology, Univ. Massachusetts, Amherst, MA, 01003); Norkin, L. C. *Virology* 91(1): 194-197; 1978.

An assay for the rapid microtitration of simian adenovirus 7 (SA7) particles capable of inducing an adenovirus cytopathic effect (rounded, swollen cells) is described. Utilizing this assay for cytopathic particles, it was found that only one passage of standard SA7 at a high multiplicity of infection (moi) resulted in virus stocks containing an excess of noninfectious cytopathic particles. These stocks also contained an excess of defective virions that retained the ability to enhance the replication of human adenovirus type 5 during mixed infection of monkey cells. SA7 stocks produced on two simian virus 40-transformed simian cell lines contained larger fractions of these defective virions than stocks produced on normal cell lines. Autointerference activity was not observed in SA7 stocks containing an excess of defective cytopathic particles, and there were no detectable levels of shortened viral genomes. The results indicate that SA7 stocks containing an excess of defective particles are readily produced during only one passage at high moi. There need not be a drop in viral yields during subsequent passages to indicate that this phenomenon is occurring. (20 refs)

78-6969 **Phosphorylation of Chromatin- and Ribosome-associated Proteins in Cells Transformed by Adenovirus, Murine Sarcoma Virus, and Methylcholanthrene.** (Eng) Segawa, K. (Inst. Medical Science, Univ. Tokyo, Minato-ku, Tokyo 108, Japan); Oda, K.; Yuasa, Y.; Shiroki, K.; Shimojo, H. *J Virol* 27(3): 800-808; 1978.

The patterns of phosphorylation of chromatin- and ribosome-associated proteins in cells transformed by adenovirus

type 12 (Ad12), murine sarcoma virus (MSV), or methylcholanthrene (MC) were studied. A highly phosphorylated 90,000-dalton (90K) protein was detected in chromatin and ribosomes from Ad12-transformed WJ1, GY1, CY1, and WY3 cells; MSV-transformed H-NRK, K-BALB/3T3, and XC cells; MCA-transformed TCL15 mouse cells; and simian virus 40-transformed T22 monkey cells. The phosphorylated 90K protein was not detected in untransformed NRB, 3Y1, NRK, MV1Lu, or C3H.10T1/2 cells or in S+L-Mi mink cells transformed by Moloney MSV. The S+L-Mi cells showed rapid reversion to a normal morphology after several subcultures while continuing to contain rescuable MSV. The pattern of phosphorylation of proteins other than 90K in these cells resembled that of transformed rather than untransformed cells. Some 90K proteins became detectable in some untransformed cells that were stimulated to grow to the high density characteristic of transformed cells. Peptide map analysis indicated that the 90K protein of the transformed cells was similar irrespective of species of cell or transforming agent. The data suggest that the alteration in the pattern of endogenous protein phosphorylation in the chromatin and ribosomes is closely related to the transformed state of cells. (20 refs.)

78-6970 **Characterization of Adenovirus Type 12 Tumour Antigen Produced in Chick Fibroblasts.** (Eng) Pusztai, R. (Inst. Microbiology, Univ. Medical Sch., H-6720 Szeged, Hungary); Tarodi, B.; Beladi, I. *J Gen Virol* 41(2): 433-436; 1978.

The type-specific tumor (T) antigen produced in adenovirus 12 (Ad12)-infected nonpermissive chick fibroblasts and permissive HEp-2 cells was characterized by immunoprecipitation with normal hamster serum and anti-T serum and sodium dodecyl sulfate-polyacrylamide gel electrophoresis. The anti-T serum precipitated a polypeptide with an apparent mol wt of 50,000 and a smaller polypeptide of mol wt approx 11,000 from the infected HEp-2 and chick cells extracts. There was a considerably lower amount of the larger polypeptide in the chick cells than in the HEp-2 cells. These polypeptides were also obtained in the presence of 50 μg/ml cytosine arabinoside, but they were not observed when normal hamster serum was used or when mock-infected chick fibroblast extract was precipitated by anti-T serum. It is concluded that the size of the major component of Ad12-specific T antigen is 50,000 daltons. (8 refs)

78-6971 **Poliovirus Single-stranded RNA and Double-stranded RNA: Differential Infectivity in Enucleate Cells.** (Eng) Detjen, B. M. (Dept. Biology, Washington Univ., St. Louis, MO, 63130); Lucas, J.; Wimmer, E. *J Virol* 27(3): 582-586; 1978.

The ability of single-stranded poliovirus virion RNA (PV-RNA) and double-stranded poliovirus replicative form (RF) RNA to replicate in enucleated mouse L cells was investigated. Monolayers containing >99% enucleated L cells were prepared by cytochalasin B (10 μg/ml) treatment in conjuntion with centrifugation. Control nucleate cells were prepared by similar treatment with cytochalasin B and omission of the centrifugation step. Virion RNA replicated successfully in the absence of the cell nucleus, but RF RNA did not produce any detectable progeny in enucleated cells. The results show that the nucleus is involved in RF RNA infection, presumably in the early stages. (47 refs)

78-6972 **Poly(C)- and Poly(G)-rich Tracts in the RNA of Oncornaviruses.** (Eng) Phillips, L. A. (Lab. Viral Carcinogenesis, NCI, Bethesda, MD, 20014); Pang, R. H. *In: Third International Symposium on the Detection and Prevention of Cancer held by the International Study Group for the Prevention and Detection of Cancer in New York, April 26-May 1, 1976.* International Study Group for the Prevention and Detection of Cancer (New York, NY): Vol. 1(part 1): 1193 pp.; 311-319; 1977.

Evidence is given for the presence of poly(C)- and poly(G)-rich tracts in both untreated and RNase T_1- and RNase C-treated [dimethyl-^{3}H] viral RNA of avian, murine, hamster, feline, and primate oncornaviruses (OV's) as detected by polynucleotide agarose affinity columns. This finding demonstrates the universality of these tracts in the RNA of leukemia and sarcoma viruses. The tracts may play a genomic stabilizing role in OV RNA, and they may also play a role in the transcription of OV RNA. Poly(C) may be involved in the replication of some other viruses, as encephalomyocarditis virus-infected cells contain a viral specific polymerase that can use poly(C) homopolymers as templates, and poly(C) homopolymers can also serve as templates for Qβ replicase. If it can be determined that OV RNA contains specific polynucleotide sequences or tracts that are not present in nonviral messenger RNA (mRNA) of human cells, it may be possible to make sequence-specific drugs against the unique viral-specific polynucleotide sequences or tracts to block transcription of viral RNA into viral DNA by reverse transcriptase and to block translation of viral RNA into viral proteins by the cellular ribosomes, while not affecting the translation of cellular nonviral mRNA into cellular proteins. Thus, a possible molecular approach to cancer therapy may become a reality. (27 refs)

78-6973 **DNA Polymerase Reactions in Human Bladder Tumor Cells in Culture: Characterization of the RNA-associated Product.** (Eng) Davis, A. R. (Dept. Microbiology and Immunology, Univ. California Sch. Medicine, Los Angeles, CA, 90024); Vayuvegula, B. S.; Nayak, D. P. *In: Third International Symposium on the Detection and Prevention of Cancer held by the International Study Group for the Prevention and Detection of Cancer in New York, April 26-May 1, 1976.* International Study Group for the Preven-

and Detection of Cancer (New York, NY): Vol. 1(part 193 pp.; 17-26; 1977.

RNase-sensitive endogenous DNA polymerase activity ined in the cytoplasmic pellet fraction of cultured T-24 derived from a human transitional cell carcinoma of the der was partially characterized. Pretreatment of the cyto- nic pellet with RNase reduced the activity threefold, and eaction was inhibited 80% by actinomycin D (AD). The ion kinetics were linear for 5 min only. Analysis of the A product of 5-min reactions, prepared in the presence D, by Cs_2SO_4 equilibrium-density gradient centrifugation led a nucleic acid product migrating as 10%-47% RNA sity 1.63) and 30%-70% DNA (density 1.39-1.42). Less 1% of the product prepared under the same conditions T-24 nuclei or mitochondria or from the cytoplasmic t fracton of WI-38 cells, a normal human diploid cell migrated as RNA. The label in the RNA region of the O_4 gradients no longer migrated as RNA after treatment e total product with high- and low-salt RNase or S-1 ease. Under conditions in which hybrids are maintained -salt RNase or S-1 nuclease), small amounts of material seen migrating in the hybrid region of the gradients. ent ^{3}H-DNA recovered from the RNA region of the ient was partially resistant to S-1 nuclease. Thus, part e RNA-associated DNA product was a RNA-DNA hy- and part was single-stranded DNA. Known RNA tumor es catalyze the transcription of RNA to DNA via re- transcriptase, with early products being RNA-DNA ids. The DNA polymerase reaction product migrating NA and other properties of the reaction indicate that an enzyme is present in the T-24 cells. (31 refs)

974 **Ultrastructural Study of Virus-like Particles in Chinese Hamster Lung Cells.** (Eng) Calafat, J. Virology, The Netherlands Cancer Institute, 108 Sar- istraat, Amsterdam, Netherlands); Hilkens, J. G. *J Gen* 41(2): 417-420; 1978.

s-like particles found in the E36 cell line derived from ese hamster lung cells are described. Two kinds of parti- were found: viruslike particles in the cytoplasm associat- ith the centrioles, and extracellular viruslike particles mbling the immature and mature forms of the on- uses but different from the classical B- and C-type parti- Apparently, the intracytoplasmic, budding, immature, mature particles noted were different stages in the mor- genesis of the same virus. No major C- or B-type virus eins were detected, indicating that there was no immuno- al relationship between the virus characterized and pe virus from mammals or mouse B-type virus. (12 refs)

975 **Transformation of Normal Bone-Marrow Cells by a Leukaemic Cell Line Associated with a Presumptive New Human Virus.** (Eng) Karpas, A. (Dept. Haematological Medicine, Univ. Cambridge Clinical Sch., Hills Road, Cambridge, England); Wreghitt, T. G.; Nagington, J. *Lancet* 2(8098): 1016-1019; 1978.

Experiments were carried out to determine whether the intracytoplasmic leukoviruslike bodies found in the cells and culture medium of a T-cell lymphoblast line established from a leukemic patient could transform normal human bone marrow cells in vitro. The leukemic cell line (241 cells) was initiated from the buffy coat of a man with terminal acute monocytic leukemia superimposed on a longstanding non-Hodgkin's lymphoma. When the cells were lethally irradiated and added to normal bone marrow cells from a female donor, the latter were transformed into continuous replication, and they produced the same types of viruslike particles. The new cell line (P2-241), which has been in continuous culture for 4 mo, consists of female B lymphoblasts quite distinct from the male T-cell line 241. Sectioned cells of the nonirradiated line 241 and marrow line P2-241 contained two types of round viruslike particle in the Golgi region, one approx 50 nanometers (nm) and the other 70 nm in diameter. Formation of 50-nm particles by intracytoplasmic budding was observed. It appears that marrow cells are transformed in vitro to continuous replication by the 241 cell line. (10 refs)

78-6976 **Reverse Transcriptase Activity in Extracts of Human Prostatic Tissues.** (Eng) Job, L. (Dept. Medical Viral Oncology, Roswell Park Memorial Inst., Buffalo, NY); Carter, W. A.; Arya, S. K. *Oncology* 35(5): 202-205; 1978.

Three types of human prostatic tissue (normal, hyperplastic, and adenocarcinoma) were examined for particle-associated reverse transcriptase (RT) activity. The activity was isolated by banding the tissue extract in an equilibrium sucrose density gradient followed by phosphocellulose chromatography of the lysate of material banding at 1.14-1.20 g/ml. It was characterized by its utilization of poly(Cm), which is a specific template for oncornaviral RT, and by its inhibition by selective inhibitors of viral RT, such as poly(Am) and poly(I). The activity did not utilize synthetic DNA templates, such as poly(dA):oligo(dT) and poly[d(A-T)], which is consistent with the interpretation that the DNA polymerase activity isolated from prostatic tissue is a RT. Of the tissues examined, 1/4 normal, 5/6 hyperplastic, and 2/2 adenocarcinoma specimens contained viruslike RT activity. These results suggest that oncornaviruses may be associated with the human prostate. (18 refs)

78-6977 **Inclusion Bodies Containing Virus-like Particles in Acute Lymphocytic Leukaemia of Childhood.** (Eng) Smith, H. (Dept. Pathology, Royal Brisbane Hosp., Queensland 4029, Australia). *Leuk Res* 2(2): 133-140; 1978.

Lymphoid cells from 28 children with acute lymphocytic leukemia (ALL) and from three control groups (children with acute nonlymphocytic leukemia or nonleukemic malignancies and normal children) were examined for the presence of distinctive cytoplasmic inclusions. Light microscopy revealed such inclusions (0.7-7.6 μm) in 12/28 ALL patients. The inclusions tended to be close to the nucleus or were attached to it by a stalk. Inclusions were not seen in nonlymphoid cells; they were more frequent in leukemic than in nonleukemic lymphocytes, and more frequent in marrow than in blood cells. In all other patients with inclusions, they were found only in leukemic cells. Inclusions were more frequent in necrobiotic cells than in viable lymphoid cells in blood but not marrow of one patient. Electron microscopy showed that the inclusions are enclosed particles with a membrane usually 10-30 nanometers (nm) thick but in some cases up to 100 nm thick. Budding from the inside of the enclosing membrane was suggested by connection between it and some particles and by clustering of particles around some villi. Inclusions similar to those in ALL were seen rarely in normal lymphocytes and in acute nonlymphocytic leukemic cells, but they were seen often in nonleukemic malignancies. Profusely populated groups (≥20 particles in a profile) and villous intrusions of the enclosing membrane occurred only in the ALL patients. The particles do not resemble known viruses, but some characteristics suggest that they have a viral nature. (23 refs)

See also:
*(Rev.): 78-6610, 78-6616, 78-6620, 78-6632, 78-6639, 78-6661, 78-6669, 78-6670, 78-6671, 78-6672, 78-6673, 78-6674, 78-6675, 78-6676, 78-6677, 78-6678, 78-6679, 78-6680, 78-6682, 78-6683, 78-6684, 78-6685, 78-6686, 78-6697, 78-6978, 78-6982, 78-6983, 78-6984, 78-6985, 78-6989, 78-7005, 78-7006, 78-7008, 78-7015, 78-7016, 78-7017, 78-7018, 78-7021, 78-7023, 78-7024, 78-7029, 78-7034, 78-7036, 78-7038, 78-7045, 78-7050, 78-7065, 78-7068.
*(Path.): 78-7073, 78-7082, 78-7084, 78-7101, 78-7118, 78-7124.

6978 **A Serum Inhibitor of Cell Mediated Immunological Functions in Healthy Mice and Possible relations with C-Type Viral Expression and Spontaneous plasia.** (Eng) Krueger, J. G. (Thorman Cancer Res. Lab., ity Univ., San Antonio, TX, 78284); Moyer, R. C. *In: rd International Symposium on the Detection and Preven- of Cancer held by the International Study Group for the vention and Detection of Cancer in New York, April May 1, 1976.* International Study Group for the Preven- and Detection of Cancer (New York, NY): Vol. 1(part 1193 pp.; 409-427; 1977.

a suggesting the presence of an inhibitor of cell-mediated munological functions in the serum of healthy DBA/2J e possessing latent C-type leukemia virus are presented. phytohemagglutinin responsiveness (PHAR) of peri- al lymphocytes in a whole blood culture was measured H-thymidine uptake in nine inbred strains of mice. High low PHAR was seen in different strains, even though phocytes were taken from 14-wk-old sex-matched mice. high responders showed no C-type virus expression; e of the low responder strains showed C-type virus ression throughout their lives. The low PHAR of these ins was investigated further using low-responder DBA/2J e plus high-responder C57BL/6J mice for comparison. low responsiveness of DBA/2J mice was not related to se-response factor, to a time shift in response to PHA, o age. Splenic lymphocytes showed good PHAR, ruling the possibility of an intrinsic cellular defect. Low respon- serum reduced the PHAR of syngeneic splenic lym- cytes, and splenic lymphocytes failed to incorporate PHA actively in the presence of this serum. C57BL/6J m showed no significant inhibiting effect on allogeneic yngeneic lymphocytes. C57BL/6J serum increased the onse of C57BL/6J splenic lymphocytes to tumor-as- ated antigens from a syngeneic mammary carcinoma by 00%. DBA/2J serum prevented the response of DBA/2J nic lymphocytes to syngeneic tumor-associated antigens. ability of lymphocytes to perform cell-mediated func- s may be inhibited by factors in the serum of healthy e. (22 refs)

6979 **Influence of a Mixture of Chemical Protectors on the Lymphoid Regeneration of Bone Marrow Thymus in Irradiated Mice.** (Eng) Delrez, M. (Labora- e d'Anatomie Pathologique, Institut de Pathologie, Uni- ite de Liege, B-4000 Liege, Belgium). *Experientia* 34(9): 1-1222; 1978.

effect of chemical radioprotectors on the lymphoid peak one marrow and on the thymic cell population was determined in female C57BL mice. At 25 min before x-irradiation (400 or 650 R), the mice received 15 mg glutathione po; 10 min later, they received 8.5 mg cysteine ip followed 5 min later by ip injection of a mixture of 1.4 mg 2-β-aminoethylthiouroneum, 3 mg cysteamine, and 0.65 mg 5-hydroxytryptamine. Administration of the chemical protectors without subsequent irradiation had little effect on the bone marrow but induced a significant decrease in thymocyte number. Administration of the protectors before irradiation permitted a better bone marrow repopulation and reduced late thymic atrophy (a condition that precedes the appearance of thymic lymphomas), compared with the effects of the radiation in nonprotected animals. The lymphoid peak was considerably increased in the radioprotected animals. Thus, under conditions that were previously shown to reduce the development of lymphomas, a lymphoid rebound appeared in the bone marrow. (8 refs)

78-6980 **Electronic Cell Volume Analysis of Growth and Rejection of EL-4 Ascites Tumor Cells.** (Eng) Zucker, R. M. (Papanicolaou Cancer Res. Inst., P.O. Box 236188, Miami, FL, 33123); Harari, J.; Finley, J.; Kambour, M. *Am J Vet Res* 39(10): 1710-1712; 1978.

The in vivo growth of EL-4 leukemia cells in the peritoneal cavities of syngeneic (C57BL/6) and allogeneic (DBA/2) mice was monitored daily by electronic cell volume and cell number analysis, cell morphology, and labeling index. In C57BL/6 mice, tumor cell number increased from 2 x 10^8 to 8 x 10^8, cell volume decreased from 440 to 360 μm^3, and the labeling index decreased from 57% to 20% from days 5 to 9 after inoculation. The volume decrease was correlated with an increased cell cycle time and a decreased proliferating fraction. During the later stages (10-15 days) of EL-4 ascites tumor growth in these mice, the cell number remained constant but the cells continued to grow and divide. In DBA/2 mice, rejection of tumor cells began on day 7 after inoculation; cell number decreased from 4.6 x 10^8 to 2.5 x 10^8 cells, modal population volume from 370 to 355 μm^3. The degree of rejection was determined by electronic index; these variables were not uniform among the mice. Concomitant with the decrease in cell number and labeling index seen between days 7 and 8, the number of lymphocytes, macrophages, and dead tumor cells increased. The size of the lymphocytes was 240 μm^3, and that of the macrophages and dead tumor cells was 640-1,280 μm^3. Lymphocyte volume decreased during the rejection process until it was 110 μm^3 at complete rejection. These results demonstrate that electronic cell volume analysis can be used to study the influx of different cell types during the rejection as well as the growth of tumor cells. (12 refs)

78-6981 **Complete Tumor Inhibition by a Physiological Factor in Cell-Free Tumour Ascites.** (Eng) Kapp, J. F. (Schering AG, Research Labs., Mullerstrasse 170, 1000 Berlin 65, W. Germany). *In: The Macrophage and Cancer. Proceedings of the European Reticuloendothelial Society. Symposium held in Edinburgh, September 12-14th, 1977.* Univ. Edinburgh. (Edinburgh, Scotland): pp. 285-291; 1977.

Anti-inflammatory activity was demonstrated in mouse and rat cell-free tumor ascites fluids. Ascites from Ehrlich (including diploid and tetraploid), L1210, Krebs, and Yoshida mouse tumors and from Yoshida hepatoma, Yoshida sarcoma, and Zajdela hepatoma rat tumors were tested in the carrageenan NMRJ mouse paw edema test. Mouse tumor ascites inhibited the inflammation reaction from 40.5% to 58.5%, rat tumor ascites from 28% to 45%, but normal sera from either species were inactive. There were no inflammatory cells in the site of the inflammatory stimulus. With respect to antitumor activity, tumor growth was inhibited completely when 1 ml tumor ascites was injected ip 24 hr before ip injection of 1 x 10^5 tumor cells. An inoculum of 3 x 10^5 DBA/1J mammary adenocarcinoma cells injected sc into NMRJ mice and grown to 5 mm in diameter underwent continuous regression when 1 ml L1210 ascites fluid was injected. Likewise, human HeLa cells (1 x 10^5) injected ip into nu/nu mice were inhibited by injection of the mice with 1 ml Yoshida ascites 24 hr previously, demonstrating interspecies protection. Because sensitized lymphocytes from spleens and lymph nodes did not demonstrate cytotoxic activity in a ^{51}Cr-release assay, inhibition of tumor growth apparently occurs by stimulation of nonspecific host defense mechanisms. (9 refs)

78-6982 **Anti-viral Activity Induced by Culturing Lymphocytes with Tumor-derived or Virus-transformed Cells. Identification of the Anti-viral Activity as Interferon and Characterization of the Human Effector Lymphocyte Subpopulation.** (Eng) Trinchieri, G. (Swiss Inst. Experimental Cancer Res., Epalinges, CH 1066, Switzerland); Santoli, D.; Dee, R. R.; Knowles, B. B. *J Exp Med* 147(5): 1299-1313; 1978.

The viral inhibitor(s) released in the supernates of mixed cultures of mouse or human lymphocytes and certain tumor-derived or virus-transformed mouse or human cell cultures was characterized. The inhibitor thus induced proved to be a protein that was active against a variety of unrelated viruses and was not toxic for cells. It did not directly inactivate viruses but inhibited viral replication via an intracellular mechanism that involved RNA and protein synthesis by the cells. The inhibitor was identified as interferon, which was contained in at least two molecular species, of approx 25,000 and 45,000 daltons, respectively. The supernates of the mixed cultures also displayed an anticellular activity and an ability to inhibit DNA synthesis and cell multiplication. The antiviral and anticellular activities were positively correlated in supernates from various mixed cultures and in partially purified preparations. The human cell population involved in interferon production was composed primarily of Fc receptor-positive, surface immunoglobulin negative, non-T-cell lymphocytes. The ability of certain cell lines to induce interferon was significantly associated with tumor origin or with in vitro transformation by certain viruses (Epstein-Barr virus, murine sarcoma virus). (56 refs)

78-6983 **Anti-viral Activity Induced by Culturing Lymphocytes with Tumor-derived or Virus-transformed Cells. Enhancement of Human Natural Killer Cell Activity by Interferon and Antagonistic Inhibition of Susceptibility of Target Cells to Lysis.** (Eng) Trinchieri, G. (Swiss Inst. Experimental Cancer Res., Epalinges, CH 1066, Switzerland); Santoli, D. *J Exp Med* 147(5): 1314-1333; 1978.

The effects of the interferon produced in mixed cultures of human lymphocytes and human tumor-derived or virus-transformed lines on the two cell populations were studied. Interferon preparation increased by severalfold the nonspecific cytotoxicity of human lymphocytes, the effector cells being cytotoxic for any target cell line tested and the enhanced cytotoxicity lasting for 2-3 days. The activity of spontaneous (natural) killer lymphocytes was not separable from the cytotoxic activity induced by the interferon preparations, suggesting that the interferon enhanced the activity of the natural killer cells rather than generating a new population of effector cells. In the mixed cell cultures in which interferon was produced, the interferon mediated an enhanced cytotoxicity representing up to 70%-90% of the observed cytotoxicity. The effect of interferon on the target cells was antagonistic to its effect on the lymphocytes, the susceptibility of various cells to cell-mediated lysis being decreased and in some cases almost completely suppressed after pretreatment with interferon. Interferon rendered target cells resistant to natural killer cells via an intracellular mechanism requiring RNA and protein synthesis. Virus-infected cells and most tumor cells were not similarly protected by interferon. It is suggested that interferon might render the natural killer cell system an inducible selective defense mechanism against tumor and virus-infected cells. This might occur by stimulation of efficient nonspecific cytotoxic cells and by protection of normal cells from lysis. (56 refs)

78-6984 **Increases and Perturbations in Thymocytes Forming Spontaneous Rosettes During Viral and Chemical Oncogenesis in Hamsters.** (Eng) Leffell, M. S. (Clinical Micro Lab., North Carolina Memorial Hosp., Univ. North Carolina, Chapel Hill, NC, 27514); Coggin, J. H. *Clin Immunol Immunopathol* 11(3): 275-287; 1978.

Because spontaneous (E) rosette formation with sheep RBC has been linked to diseases that involve deficient cellular immunity including malignancies, thymocytes from strain LVG Syrian golden hamsters were tested for their ability to form

osettes with sheep RBC. Preliminary studies revealed an sual seasonal variation in the percentage of rosette-form- cells (RFC) (17.2% formation in winter, compared with in later summer and fall). Further studies showed that, ardless of the seasonal variation, the number of RFC in- ased during viral and chemical carcinogenesis. Infection eonate hamsters with simian virus 40 or adenovirus 13 lted in a 50% or greater increase in RFC in thymuses ndividual hamsters assayed as early as a 2 wk postinfec- . Treatment of weanling hamsters with dimethylbenz- nthracene resulted in significant increases in thymocyte C at the time of primary sarcoma appearance. The car- ogen-induced RFC increases appeared to be limited to a ll subset of thymocytes that reacted in dextran-containing dium, compared with a larger population that bound ep RBC in the presence of heat-inactivated, sheep C-absorbed serum. In the thymocyte subset, the increases RFC were most marked after primary tumor induction. sively transferred tumor cells had only a slight effect on C values. (19 refs)

6985 **Immune Response of the Syrian Golden Hamster to SV40 Induced and Transplantable Tu- rs.** (Eng) Goldrosen, M. H. (Dept. Surgical Oncology, Tu- r Immunology Group, Roswell Park Memorial Inst., Falo, NY, 14263); Dent, P. B. *Fed Proc* 37(7): 2092-2095; 8.

e effector mechanisms that are operative against the wth of simian virus 40 (SV40)-induced tumors were inves- ted. Cell-mediated immunity of progressor, postexcision, immune peripheral blood lymphocytes was evaluated in o by the lymphocytotoxicity assay. At a ratio of 200:1, three types of peripheral blood lymphocytes caused a sig- cant reduction in the number of H50 (SV40-transformed) get cells but did not reduce the number of hamster fibro- sts. No significant cytotoxicity was observed with these ee effector populations on BHK-21 cells, which do not ry SV40-associated antigens. Thus, cytolytic effector cells be detected at all phases of progressive tumor growth and stages of tumorigenesis evaluated. However, the presence hese cells may not reflect functional in vivo tumor rejec- n. The effects of the three sera on in vitro lymphocytotox- y were also investigated. The only situation in which um blocking factors were noted was in animals that ex- ienced a recurrence of a previously excised tumor. Serum cking factors were not present in the early and middle ges of progressive tumor growth; therefore, they could not an important factor in the critical early stages of tumor wth. Serum taken from hamsters shortly after inoculation h H50 cells but before the clinical appearance of the tumor nonstrated characteristics similar to those of serum taken m immunized hamsters. These sera augmented the cyto- ic reactivity of tumor immune lymphocytes in vitro and o induced normal lymphocytes to specifically kill tumor ls. These findings suggest that progressive primary tumor wth may be due to a lack of serum arming and potentiat- ing activity rather than the presence of serum blocking factors. On the other hand, serum blocking factors may correlate with the presence of recurrent or metastatic disease rather than with progressive tumor growth alone. (25 refs)

78-6986 **Studies of Effector Cell, Antibody, and Target Cell Interactions in Natural Cell-mediated Cytotoxicity.** (Eng) Koide, Y. (Dept. Surgery, UCLA Sch. Medicine, Univ. California, Los Angeles, CA, 90024); Kwok, R.; Takasugi, M. *Int J Cancer* 22(5): 546-551; 1978.

IgG antibodies bound to effector lymphocytes obtained from human peripheral blood through Fc receptors were observed to determine the specificity of natural cell-mediated cytotoxicity (NCMC) against cultured target cells, including sheep RBC (SRBC), antilymphocyte serum-treated lymphocytes, and a lymphoblastoid cell line. When effector cells, which possessed natural antibodies specific for antigens on cultured cells but lacked IgG antibodies specific for antigens on SRBC, were incubated in IgG anti-SRBC, they became specifically cytotoxic to SRBC. As a result of this gained specific cytotoxicity, NCMC and antibody-dependent CMC was diminished, suggesting that natural antibodies were displaced and Fc receptors on effector cells occupied by IgG anti-SRBC. It is concluded that treatment of effector cells with serum may result in increased or decreased cytotoxicity, depending upon the serum composition of specific antibodies. This type of modulation has important implications for antibody regulation of CMC (blocking and unblocking). (23 refs)

78-6987 **Spontaneous and Antibody-dependent Cell-mediated Cytotoxicity by Human T Cell Subpopulations.** (Eng) Gupta, S. (Memorial Sloan-Kettering Cancer Center, New York, NY, 10021); Fernandes, G.; Nair, M.; Good, R. A. *Proc Natl Acad Sci USA* 75(10): 5137-5141; 1978.

Human peripheral blood non-T cells, T cells, and their subpopulations (Tμ, Tγ, Tϕ, Tγ-depleted cells, and Tμ-depleted cells) were assayed for their ability to mediate spontaneous lymphocyte-mediated cytotoxicity (SLMC) against K562 tumor cells and antibody-dependent cellular cytotoxicity (ADCC) against chicken RBC coated with antibody. (Tμ = T cells with receptors for IgM; Tγ = T cells with receptors for IgG; Tϕ = T cells without receptors for IgM or IgG.) Non-T cells and purified T cells mediated both ADCC and SLMC. Depletion of Tμ cells did not influence these activities, whereas depletion of Tγ cells resulted in almost complete loss of both activities. Isolated Tμ cells and Tϕ cells did not demonstrate significant ADCC or SLMC activity, and Tγ cells demonstrated strong SLMC activity but did not demonstrate significant ADCC activity. The data demonstrate that SLMC and ADCC activities in T lymphocytes are mediated by Tγ cell subpopulatons. The two cytotoxic reactions may be mediated by two distinct subsets of Tγ cells or by a single effector cell type using two different mechanisms. (54 refs)

78-6988 **Cytotoxic Activity of Guinea-Pig Lymph-Node Cells Stimulated In Vitro.** (Eng) Altman, A. (Dept. Cellular and Developmental Immunology, Scripps Clinic and Res. Foundation, 10666 N. Torrey Pines Road, La Jolla, CA, 92037); Rapp, H. J. *Int J Cancer* 22(5): 595-601; 1978.

Several stimulators of lymphocyte proliferation were tested for their capacity to induce strain 13 guinea pig lymph node cells (LNC) to become cytotoxic in vitro. The stimulating agents were 5% fetal calf serum; 5 x 10^5 M 2-mercaptoethanol; 1.6 x 10^5 virally induced, syngeneic, 543 sarcoma cells or various amounts of allogeneic (strain 2) mineral oil-induced peritoneal exudate cells, all treated with 60 μg/ml mitomycin C; and 2.5 μg/ml phytohemagglutinin (PHA) or concanavalin A. LNC cultured in the presence of these agents were cytotoxic to normal syngeneic fibroblasts and to syngeneic, (13F, 543), allogenic (L1), or xenogeneic (human myeloid line K562) tumor cells, but not the PHA-induced strain 2 lymphoblasts. LNC had weak or no cytotoxic activity when freshly harvested from guinea pigs, indicating that acquisition of cytotoxicity was a result of events occurring in culture. Potentiation of cytotoxicity was accompanied by a marked proliferation of the cultured LNC; the combination of several stimulatory agents had an additive effect on the generation of cytotoxicity. (20 refs)

78-6989 **Production of Migration Inhibitory Factor (MIF) by Human Leukocytes Following Exposure to Epstein-Barr Virus.** (Eng) Wilson, G. L. (Dept. Microbiology, Univ. Maryland, College Park, MD, 20742); Young, B. G. *Cell Immunol* 38(1): 147-156; 1978.

The ability of Epstein-Barr virus (EBV) to induce a cell-mediated immune response (CMI) in cultures of human WBC was investigated. Partially purified EBV, obtained from culture fluids of AV-1 cells, was inactivated by exposure to UV radiation. Inactivated virus was mixed with peripheral WBC from Hodgkin's disease (HD), infectious mononucleosis (IM), and malignant lymphoma patients as well as from normal individuals. Production of migration inhibitory factor (MIF), as measured by guinea pig macrophage migration inhibition (MMI), was used as an indicator of CMI response. Significant differences in MIF response were observed subsequent to exposure of the cells to EBV. WBC from patients in each of the disease categories tested exhibited greater MIF production than WBC from normal controls. Furthermore, there was a significant difference between the response of IM-derived cells and the response of HD- and lymphoma-derived cells. Serum from each subject was examined for immunoglobulin specific for EBV capsid antigen (anti-VCA). Although the majority of individuals within the disease categories tested had elevated anti-EBV serum titers, no correlation could be made between elevated anti-VCA titer and levels of MIF production. (22 refs)

78-6990 **Effect of Host Inflammatory Response on the Tumorigenicity of a Mouse Melanoma (Meeting Abstract).** (Eng) Freedman, V. H. (Rockefeller Univ., New York, NY); Calvelli, T. A.; Silagi, S.; Silverstein, S. C. *J Cell Biol* 79(2, part 2): 91a; 1978. (no refs)

78-6991 **Do Tumors Escape Surveillance by Depression of Macrophage Inflammation?** (Eng) Normani S. J. (Dept. Pathology, Univ. Florida Coll. Medicine, Gainesville, FL, 32610); Schardt, M.; Sorkin, E. *In: The Macrophage and Cancer. Proceedings of the European Reticuloendothelial Society Symposium held in Edinburgh, September 12-1 1977.* European Reticuloendothelial Society (Edinburgh Scotland): 448 pp.; 247-257; 1977.

The hypothesis that growing tumors compromise monocyt chemotaxis and decrease macrophage (MP) accumulation i inflammatory foci, thereby altering the ratio of MP to tumo cells, decreasing the probability for close contact of thes cells, and escaping growth control by MP, was investigate Nitrocellulose filter disks were inserted into the connecti tissue of DA rats with and without transplanted 7,12-dim thylbenz(a)anthracene (DMBA)-induced tumors. Twel days after transplantation, both groups showed a biphas pattern of MP accumulation, but in tumor-bearers both th total number of cells and their rate of accumulation we diminished markedly. This depression in MP accumulatio was approx 65% and it lasted for at least 5 days, despite th persistence of the inflammatory stimulus. Thus, tumor-bea ing induced a generalized defect in MP inflammation by a tering MP accumulation not only in the peritoneal cavity b also in inflamed connective tissue. The defect required th continued presence of the tumor, as it was rapidly correcte by surgical excision of the primary tumor. However, the d fect usually occurred late in tumor growth, required a thres old number of tumor cells often exceeding 100 million, an did not exist when the animal possessed latent tumor cel that remained viable following surgical resection of the pr mary tumor. Thus, it is concluded that the defect in monocy inflammation arises as a result of neoplastic progression an that it is not a factor that limits surveillance or contribut to the emergence of nascent cancer cells. (27 refs)

78-6992 **Inflammation and Activation of Macrophage** (Eng) Fauve, R. M. (Unite d'Immunophysiol gie Cellulaire, Institut Pasteur, 25 Rue du Dr. Roux, 7501 Paris, France); Hevin, M. B.; Dauge, M. C. *In: The Macr phage and Cancer. Proceedings of the European Reticuloend thelial Society Symposium held in Edinburgh, Septemb 12-14, 1977.* European Reticuloendothelial Society (Edi burgh, Scotland): 448 pp.; 258-263; 1977.

C57Bl mice were highly resistant to challenge with virule *Listeria monocytogenes, Schistosoma mansoni,* and the Lew lung carcinoma (LLC) when inflammatory reactions wer induced previously at a distance from the site of infection b injecting the dorsal area sc with magnesium silicate embe ded in calcium phosphate gel. When *L. monocytogenes* w

ected iv (10 LD_{50}), mice with the inflammation had 10^3 and less organisms in spleen and liver on the third day than ntrol mice. Similarly, mice with an inflammatory reaction re free of worms 45 days postinfection with 100 furcocer-iae of *S. mansoni.* When 10^6 LLC cells were injected into rear left footpad 4 days before or 4 days after induction the inflammatory reaction, tumor growth was delayed. No tastases were found in the lungs of treated mice 20 days er LLC inoculation. When mice received 10^6 LLC cells in sternal area one day before inflammation induction, tastases were delayed and there were many WBC and mac-phages among the tumor cells. These results suggest that me sort of serum mediator acted on the pathogens, since se were never in physical contact with the inflammatory ction. (10 refs)

-6993 **Regulation of Macrophage Tumoricidal Function: A Role for Prostaglandins of the E Series.** ng) Schultz, R. M. (Lab. RNA Tumor Viruses, NCI, Be-sda, MD, 20014); Pavlidis, N. A.; Stylos, W. A.; Chirigos, A. *Science* 202(4365): 320-321; 1978.

e ability of several agents to interfere with macrophage tivation by interferon (IF) preparations in vitro was mea-red using macrophages from male $CD2F_1$ mice. IF (1,000 its/ml culture medium) was added to the macrophage cul-es for 16 hr. Agents tested for inhibitory action were added 100-μl portions. Treated macrophages were tested for totoxicity to MBL-2 lymphoblastic leukemia cells. IF-ac-ated macrophages suppressed leukemia cell growth at 48 by 67%. When prostaglandin E_1 or E_2 was added simul-neously with IF to resting macrophages or for 2 hr after treatment, the tumoricidal activity of the macrophages s inhibited. A prostaglandin concentration of $> 10^{-7}$ M s necessary for macrophage suppression. Prostaglandin F_2 s ineffective at all concentrations tested when added nultaneously or after IF treatment. Dibutyryl cyclic AMP d hydrocortisone also decreased macrophage tumoricidal tivity. Subsequent treatment of IF-activated macrophages th dibutyryl guanosine 3′,5′-monophosphate (GMP), in-methacin, or colchicine did not influence macrophage moricidal function. The regulation of macrophage function IF and prostaglandin E may occur through a balance in clic AMP- and cyclic GMP-associated signals. Direct evi-nce for this conclusion awaits corroboration of levels of clic nucleotides in the macrophages with the observed ef-cts of the agents tested. (22 refs)

-6994 **Striking Differences in Interaction Between Macrophages and Two Closely Related Tumor nes.** (Eng) Kaplan, G. (Dept. Morphology, Inst. Medical ology, Tromso, Norway); Seljelid, R. *In: The Macrophage d Cancer. Proceedings of the European Reticuloendothelial ciety Symposium held in Edinburgh, September 12-14, 77.* European Reticuloendothelial Society (Edinburgh, otland): 448 pp.; 347-363; 1977.

A murine methylcholanthrene-induced solid sarcoma (MSS), its ascites form (MAA), and a solid tumor line derived from it (MAS) were used to study the in vitro interaction of syngeneic mouse macrophages with the tumor cells from intraperitoneal transfers. After sc or ip injection into C_3H mice or their F_1 hybrids, MSS cells yielded solid tumors which metastasized efficiently. MAS cells injected sc yielded solid tumors and injected ip yielded nonmetastasizing ascites when injected ip. Ascites from the mice which developed them were grown in culture. Macrophages from the MAA cultures became activated as indicated by their morphology and ability to ingest complement-coated particles. The macrophages proliferated and inhibited tumor cell growth; macrophage proliferation then decreased as the tumor cells died. The presence of tumor cells was apparently required for macrophage activation, and the macrophages appeared to kill the tumor cells by nonphagocytic means. The MAS cells showed less macrophage activation, and tumor cell killing was not apparent. The data show a correlation between the ability of tumor cells to give rise to solid metastasizing tumors and the extent to which the tumor could be inhibited and killed in vitro by syngeneic macrophages; ie, the more aggressive tumor in vivo is less susceptible to macrophage activation and killing in vitro. (30 refs)

78-6995 **Antitumour Effects of Macrophages in BCG Contact Therapy of Rat Tumours.** (Eng) Hopper, D. G. (Cancer Res. Campaign Labs., Univ. Nottingham, Nottingham, England); Pimm, M. V. *In: The Macrophage and Cancer. Proceedings of the European Reticuloendothelial Society. Symposium held in Edinburgh, September 12-14th, 1977.* Univ. Edinburgh. (Edinburgh, Scotland): pp. 182-187; 1977.

Wistar/Nottingham rats were inoculated sc with 2 x 10^6 sarcoma Mc7 or Mc40A cells or hepatoma D23 cells, alone or in admixture with 1 mg BCG, and the cellular contents of the resulting tumors were investigated. Sarcoma cells alone produced progressively growing tumors, and the sarcoma cell: macrophage (MP) ratio was 1:0.2 for the Mc7 cells at 22 days and 1:0.4 for the Mc40A cells at 17 days. BCG + sarcoma cells, however, produced small nodular recessor tumors, and the ratios were 1:1.3 for the Mc7 cells at 22 days and 1:1.0 for the Mc40A cells at 17 days. Lymphocyte levels were similar in regressor and progressor tumors. Hepatoma D23 was not as susceptible to BCG contact therapy as the sarcomas. BCG + hepatoma cells produced tumors whose growth was progressive although retarded compared to that of tumors developing from injection of hepatoma cells alone. The hepatoma cell:MP ratio in the BCG-progressor tumors was 1:0.3 at 6 days; that in the progressor tumors developing from tumor cells injected alone was 1:0.1. These results suggest that for BCG to prevent the growth of 2 x 10^6 tumor cells, sufficient MP must be present at the tumor site. This hypothesis is strengthened by the results of experiments in which the hepatoma cell-BCG inocula was enriched with 50% MP. An increase in MP numbers to the extent that the

hepatoma cell:MP ratio was 1:1 rendered the tumor cells susceptible to BCG contact therapy; ie, it prevented their growth completely. (33 refs)

78-6996 **Stimulation of Tumor Growth in Mice by High Doses of BCG.** (Eng) Kaledin, V. I. (Inst. Cytology and Genetics, Siberian Dept. USSR Acad Sciences, Novosibirsk, 90, USSR); Kurunov, Y. N.; Matienko, N. A.; Nikolin, V. P. *J Natl Cancer Inst* 61(6): 1393-1396; 1978.

The effect of BCG vaccination on the growth of Krebs-2 carcinoma was studied in virgin female C57BL/6 (susceptible to BCG infection), CC57BR/M (resistant to BCG), and C3Hf (resistant to BCG, mammary tumor virus-free) mice. Animals were vaccinated at 2 mo of age with 0.05 mg live BCG. Thirty days later, 1 or 2 x 10^5 Krebs-2 carcinoma cells were injected im and the animals killed 15 days later. The number of living BCG in C57BL/6 mice was 30 times higher than that in C3Hf mice, and the tumors in vaccinated C57BL/6 mice were 1.5 times heavier than those in control C57BL/6 mice. The tumor wt of BCG-vaccinated and control C3Hf mice did not differ, indicating that tumor growth was stimulated only in the BCG-sensitive strain. Various doses of BCG were given to C57BL/6 and CC57BR/M mice 14 days prior to Krebs-2 transplantation. When the BCG dose was sufficiently high (1.0 mg), tumor growth was stimulated in both mouse groups. Dead mycobacteria and inert particles (India ink) promoted tumor growth, suggesting that this effect may be due to the presence of large quantities of corpuscular particles which load the macrophages and render them incapable of guarding against the transplanted tumor cells. When Krebs-2 carcinoma was transplanted in CC57BR/M mice 80 days after BCG vaccination (when no viable BCG were detected in the spleen), tumor growth was inhibited 41.5%. These results indicate that the effects of BCG are based on the diversion of effector cells (macrophages) and on the activation of pools of these cells. High doses of BCG may be dangerous in human cancer immunotherapy, and patients predisposed to cancer should be revaccinated with BCG to maintain the effector cell pool at a high level of activation. (18 refs)

78-6997 **The Effect of the Macrophage Cytotoxic Agent Iota Carrageenan on the Growth of Two Transplantable Murine Ascites Tumours.** (Eng) Pugh-Humphreys, R. G. (Dept. Zoology, Univ. Aberdeen, Tillydrone Ave., Aberdeen AB9 2TN, Scotland); Richardson, C. A.; Wilson, A. R.; Cruickshank, W. J. *In: The Macrophage and Cancer. Proceedings of the European Reticuloendothelial Society Symposium held in Edinburgh, September 12-14, 1977.* European Reticuloendothelial Society (Edinburgh, Scotland): 448 pp.; 142-154; 1977.

The role of macrophages (MP) in the growth of ascites tumor allografts in C57BL10 mice was evaluated with the use of a commercial preparation of the MP cytotoxic agent iota carrageenan (IC: Auby Gel X52). Groups of 10 mice were inocu- lated ip with 10 μg IC 24 hr before they were inoculated ip with threshold or subthreshold doses of Landschutz ascite carcinoma (LAC) or EL4 ascites lymphoma cells. In prelimi- nary experiments, light and electron microscope studies o aspirated lymphoreticular cells at varying times after ip injec tion of IC alone revealed that IC was selectively cytotoxic fo peritoneal MP but not for lymphocytes or polymorphonu- clear WBC. Injection of the tumor cells alone elicited an in- flammatory response within the peritoneal cavity, and hos lymphoreticular cells, particularly MP and neutrophils congregated around the tumor cells. In IC-treated mice, only the polymorphonuclear WBC appeared to congregate aroun the tumor cells. IC had a dose-dependent cytotoxic effect o LAC cells. Doses of 10 and 25 μg had no significant effec on tumor growth, but 50-200 μg reduced the percentage o mice that developed tumors and 500 μ-2 g inhibited tumo development completely. In contrast, IC had no deleterious effect on the viability of EL4 cells, even at high concentra tions. IC potentiated the growth and development of EL lymphomas in the mice while simultaneously killing MP Thus, MP play an important role in regulating the growth of the EL4 lymphoma in C57BL10 mice. The nature of th cytotoxic effect of IC on the LAC cells is being studied. Selec tive killing of MP may abrogate an important growth-con- trolling mechanism within the tumor-bearing host. (45 refs

78-6998 **The Effects of Altered Phagocytic Activity o Growth of Primary and Metastatic Tumour** (Eng) Sadler, T. E. (Urology and Transplant Unit, Dept Surgery, Royal Postgraduate Medical Sch., Hammersmith Hosp., London, W12 OHS, England); Jones, P. D. E.; Castro J. E. *In: The Macrophage and Cancer. Proceedings of th European Reticuloendothelial Society Symposium held i Edinburgh, September 12-14, 1977.* European Reticuloendo thelial Society (Edinburgh, Scotland): 448 pp.; 155-163; 1977

Silica (Si), cortisone acetate (CA), trypan blue (TB), diethyl stilbestrol (DES), and *Corynebacterium parvum* were used i macrophage phagocytosis studies that determined an invers relationship between phagocytic index and metastatic behav ior of tumors, but no apparent relationship between primary tumor growth (as measured by size) and phagocytosis. Si giv en iv (0.1 ml) and ip (0.5 ml) 3 hr later on days 4 and 9 afte sc implantation of the Lewis lung carcinoma in the lowe flank of C57Bl/10 ScSn mice depressed the phagocytic inde and significantly increased pulmonary metastases above con trol values. Similar results were obtained with CA (0.1 ml sc given on days 4 and 11 after tumor transplantation. DES (0. ml sc) given on days 0-4 after tumor inoculation and TB (0. ml ip 24 hr and 0.1 ml ip 3 hr prior to tumor implantation had little effect on the phagocytic index values, neither com pound significantly altered the number of metastases. *C. par vum* (0.2 ml iv) given at tumor implantation caused a signifi cant rise in the phagocytic index and a significant reductio in the number of metastases and overall tumor growth. Si

and DES also decreased tumor growth, but TB had no rent effect. (30 refs)

999 **Depression of Mononuclear Phagocyte Function in C57Bl Mice Bearing Lewis Lung Carma.** (Eng) Otu, A. A. (Dept. Surgery, St. Margaret's p., Calabar, Nigeria); Russell, R. J.; Wilkinson, P. C.; te, R. G. *In: The Macrophage and Cancer. Proceedings e European Reticuloendothelial Society Symposium held dinburgh, September 12-14, 1977.* European Reticuloendelial Society (Edinburgh, Scotland): 448 pp.; 281-284; .

tudy the influence of Lewis lung carcinoma on macroge function in C57Bl mice, the effects of growing tumors, or cell extracts, and sera from tumor-bearing animals on learance of colloidal carbon from the circulation, chemos of peritoneal macrophages in vitro, and the in vitro macage colony formation capacity of bone marrow derived cells were investigated. During the first 72 hr after tuimplantation, there was a pronounced depression in all e functions. For 2 wk thereafter, all functions were nor- or above normal, but all were again severely depressed the tumors metastasized and the mice had entered the inal stage. Sera or tumor supernatant from tumor-bearmice depressed carbon clearance in normal mice and ined the in vitro locomotion of peritoneal macrophages normal mice. The data suggest that the tumor cells sed a product which circulated in the blood and which inhibitory to macrophages. (14 refs)

000 **Promotion of L1210 Tumour Growth by Macrophages.** (Eng) Huget, R. P. (Dept. Microbiolo- Lab. Immunology, Univ. Ulm, 7900 Ulm, W. Germany); l, H. D.; Opitz, H. G. *Z Immunitaetsforsch* 154(5): 441; 1978.

study the role of macrophages in tumor immunity, 10^4 10 mouse lymphoma cells derived from the peritoneal ty or from in vitro cultures were injected sc into DBA/2 e; and tumor development was monitored. Mice injected peritoneal exudate cells developed tumors within 9 days. nor incidence was reduced and tumor development yed by several days when in vitro derived cells were ined or when adherent cells were removed from the peritoly derived cells prior to injection. Addition of adherent in high numbers to in vitro derived L1210 cells acceleratumor growth, as did the addition of syngeneic liver cells. differences in tumor development among the various ups were statistically significant ($p < 0.05$). The tu-promoting effect of the adherent cells in the recipient e was apparently not due to an increased proliferative acity of the tumor cells. The data suggest that, under cer- conditions, a cell population with the functional properof macrophages is able to promote tumor development, probably due to its nonspecific effect on the microenvironment of the growing tumor. (14 refs)

78-7001 **Toxic Effects of Tumour Cells on Macrophages.** (Eng) Fauve, R. M. (Unite d'Immunophysiologie cellulaire, Institut Pasteur, 25 rue du Dr. Roux, 75015 Paris, France); Hevin, M-B. *In: The Macrophage and Cancer. Proceedings of the European Reticuloendothelial Society Symposium held in Edinburgh, September 12-14, 1977.* European Reticuloendothelial Society (Edinburgh, Scotland): 448 pp.; 264-270; 1977.

The substance(s) responsible for the toxic effects of Lewis tumor cells on peritoneal macrophages from C57Bl/6 and NCS mice was studied. Bradykinin in concentrations of 10^{-7} to 10^{-8} M increased the spreading of peritoneal exudate macrophages in vitro. In contrast, the spreading of macrophages was decreased in the presence of 0.1 μg/ml or more (up to 100 μg/ml) of the active fraction obtained from Lewis tumor cell supernatant (AP). No decrease was observed when the macrophages were exposed to the same concentrations of the 10^3- to 10^4-mol wt fraction from fetal mouse kidney cells. Also, no decrease was observed when the peritoneal cells were incubated with bradykinin and then with AP. No increase in spreading was observed when the peritoneal cells were incubated first with AP and then with bradykinin. The data suggest that tumor culture supernatants inhibit the fixation of bradykinin to macrophage membranes. (27 refs)

78-7002 **The Role of Complement Cleavage Products in Killing of Tumor Cells by Macrophages.** (Eng) Schorlemmer, H. U. (Inst. Medical Microbiology, Johannes-Gutenberg-Univ., 6500 Mainz, W. Germany); Hadding, U.; Bitter-Suermann, D.; Allison, A. C. *In: The Macrophage and Cancer. Proceedings of the European Reticuloendothelial Society Symposium held in Edinburgh, September 12-14, 1977.* European Reticuloendothelial Society (Edinburgh, Scotland): 448 pp.; 68-77; 1977.

Macrophages (MP) recovered from the peritoneal cavities of Swiss mice were cultured with pure guinea pig complement cleavage product C3b (20 μg/ml) or lipopolysaccharide (LPS: 25 μg/ml), and the effect of these substances on the capacity of MP to lyse tumor cells was determined. ^{51}Cr-labeled L 5178 YE lymphoma cells were added to the MP 24 or 48 hr after culture initiation, and both cell types were cultured together for a further 16-18 hr. Unlike unstimulated control cultures, MP incubated with C3b or LPS lysed all or nearly all of the tumor cells. The MP also lysed P-815 mastocytoma cells and human lymphoblastic cells. The mastocytoma cells appeared to be the most sensitive to the lytic effect. This effect was C3b dose- and time-dependent, and it was considerably reduced in the presence of serum. The tachyphylaxis and cross-desensitization observed with reference samples of C3a identified the active agent in the media

of stimulated MP as C3a. Further evidence that the lytic activity is due to C3a comes from experiments using specific antiserum against C3a, which is presumably released from C3b-stimulated MP. These results show that C3b is a potent naturally occurring stimulator of MP activities, including tumor cell lysis. (11 refs)

78-7003 **Tumor-induced Immunosuppression.** (Eng) Friedman, H. (Dept. Microbiology and Immunology, Albert Einstein Medical Center, Philadelphia, PA, 19141); Specter, S.; Watanabe, M.; Pan, S. H. *Am J Pathol* 93(2): 499-513; 1978.

Three tumor systems (lymphoma cell line FBL-3, mastocytoma cell line P815X, and plasmacytoma cell lines MOPC 104E, MOPC 31C, MOPC 173, and TEPC 15) were studied for their ability to modify humoral immunity to sheep RBC (SRBC) in vitro and in vivo. For the in vivo studies, BALB/c or DBA/2 mice infected with the Friend leukemia virus (FLV) complex or inoculated with tumor cells were challenged by ip or iv immunization with 4 x 10^8 SRBC. For the in vitro studies, 5 x 10^6 spleen cells from tumor-bearing or normal animals were cultured and immunized with 0.1 ml of a 0.1% suspension of SRBC (2 x 10^6 cells). FLV and all tumors depressed the hemolytic antibody plaque-forming cell response in susceptible mice, and spleen cells from normal animals were suppressed by intact tumor cells as well as by cell-free extracts from the plasmacytomas and mastocytomas. Cocultivation of FBL-3 lymphoma cells, which were initially induced by FLV in neonatal C57Bl/6 mice, also resulted in immunosuppression. However, cell-free extracts from these immunosuppressive lymphomas were nonsuppressive. Thus, the lymphoma model did not support the concept that immunosuppression always occurs as a consequence of soluble factors. The mechanisms of suppression, although not fully defined, were different for each system investigated. (32 refs)

78-7004 **Correlation Between Immunosuppression to Tumorigenesis. I. Humoral Immunosuppressing Factor.** (Eng) Hakim, A. A. (Dept. Surgery, Div. Surgical Oncology, Coll. Medicine, Univ. Illinois Medical Center, 180 Longwood Drive, Kankakee, IL, 60901). *Eur J Cancer* 14(11): 1249-1260; 1978.

The biological activities of agents released as a result of tumor cell proliferation were identified. Factors that alter cellular immunity and macrophage and lymphoid cell functions can be obtained from sera of animals bearing proliferating tumors. Inbred female Fischer rats and CFW mice bearing syngeneic mammary adenocarcinomas were used. The cytotoxicity of peritoneal macrophages and splenocytes against tumor cells and the effect of serum on the incorporation of ^{3}H-thymidine into normal splenocyte DNA in response to phytohemagglutinin (PHA) were assessed at various times during tumor growth. Serum enhanced the response of normal splenocytes to PHA if drawn before the 6th wk following sc injection of tumor cells; serum drawn after 7 wk suppressed this response. Macrophages and splenocytes from normal animals had no effect, those from animals bearing tumors enhanced tumor cell proliferation, and those from animals immunized against the tumor were cytotoxic against syngeneic tumor cells. Cell-free supernatants from mixed cultures of sensitized splenocytes, ie, splenocytes from immunized animals (at all ratios) and from animals bearing progressively growing tumors (at low ratios), with syngeneic tumor cells stimulated the response of normal syngeneic splenocytes to PHA. Since supernatants from cultures of splenocytes alone had no effect and supernatants from cultures of tumor cells alone had statistically significant suppressing activity, it is suggested that the suppressing agent(s) is released by the tumor cells. (58 refs)

78-7005 **Adjuvant-induced Thymus-derived Suppressor Cells of Cell-mediated Tumour Immunity.** (Eng) Glaser, M. (Lab. Cell Biology, NCI, Bethesda, MD, 20014). *Nature* 275(5681): 654-656; 1978.

Inoculation of mice with complete Freund's adjuvant (CFA) markedly inhibited the ability of immune spleen cells to prevent simian virus 40 (SV40)-induced tumor growth in the Winn tumor cell neutralization assay and to lyse SV40-transformed cells in the ^{51}Cr-release assay. Female (BALB/c x C57BL/6)F_1 (CBF_1) mice were inoculated ip with 0.5 ml CFA and, immediately afterward, inoculated sc with 2 x 10^7 C57SV cells (an SV40-transformed cell line of BALB/c mice). T-cell-enriched fractions of spleen cells were purified and used in the ^{51}Cr-release assay against C57SV cells. A marked depression of cell-mediated cytotoxicity was observed. Challenge, sc, of another group of mice with 1 x 10^5 MKSA cells (an SV40-transformed line of BALB/c mice) 15 days after CFA immunization or mixing T-cell-enriched spleen cells from a third group of mice with 1 x 10^5 MKSA cells and injecting this mixture sc into normal CBF_1 mice resulted in death of most of these mice from progressive tumor growth. No tumors or death occurred in untreated control animals. Similarly, in the Winn assay, inhibition of tumor cell neutralization activity of lymphocytes from CFA-treated mice resulted in tumor growth and death of all animals as opposed to untreated mice, in which tumor cell neutralization resulted in complete protection against tumor growth. Thus, CBF_1 mice challenged with syngeneic SV40-transformed cells and CFA failed to develop effector cells; instead, they developed suppressor T cells that inhibited in vivo effector T-cell functions. Adult thymectomy reversed the suppression caused by CFA, which indicates that the intact adult thymus was necessary for the induction of suppressor cells. The results suggest that there is a delicate balance between the antitumor effects of adjuvants and their immunosuppressive effects. (17 refs)

78-7006 **Enhancement of Avian Sarcoma Virus-induced Tumor Growth after Pretreatment with BCG.**

Eng) Wainberg, M. A. (Lady Davis Inst. Medical Res., Jewh General Hosp., Montreal, Quebec, Canada); Israel, E. *nfect Immun* 22(2): 328-333; 1978.

he immunoprophylactic effects of BCG and the methanol xtraction residue (MER) of BCG were investigated in chickns inoculated with avian sarcoma viruses (ASV). The chickns were inoculated in the wing web with 5 mg BCG or 0.5 ng MER 7 days before they were inoculated with 10^3 ocus-forming units of virus. Of 17 chickens inoculated with CG and ASV at the same site, 15 developed progressively rowing neoplasms that eventually led to death. Injection of CG into the wing web contralateral to that used for virus noculation or injection of MER into the same wing web did ot affect tumor development. Administration of BCG also ave rise to heightened levels of tumor-associated, cell-meiated immunity, both in chickens that received a subsequent njection of Prague strain A of Rous sarcoma virus and in ormal, BCG-inoculated controls. BCG immunostimulation s apparently restricted to the cellular immune system, since n indirect immunofluorescence assay revealed no effect of CG injection of the immunofluorescence staining capacity f virus-induced, tumor-bearing hosts. It is concluded that CG prophylaxis is stimulatory to both Rous sarcoma develpment and to antitumor immunity in tumor-bearing hosts. 20 refs)

8-7007 **Characteristic Features of Immunologically-induced Changes in the Tumorigenesis in Mice of Various Strains.** (Rus) Volegov, A. I. (Lab. Pathophysiology, P. A. Hertsen Res. Oncological Inst., Moscow, USSR). *Biull Eksp Biol Med* 86(11): 572-574; 1978.

Tumor induction was compared in 3 to 4-mo-old C3HA, C3H/He, BALB/c, C57BL/6, and random-bred mice. Mice were immunized with BCG (0.01 or 1 mg in 0.2 ml of physiological saline) or with complete Freund adjuvant (CFA; 0.02 ml). Thirteen days after CFA administration and 30 days after BCG vaccination, animals were inoculated im with 20-methylcholanthrene (20-MC; 1 mg in 0.1 ml of vegetable oil). In C3H/He mice vaccinated with BCG, tumors started to develop significantly later than in non-treated mice; in C57BL/6 mice, BCG vaccination decreased the latent period of tumor development. CFA administration decreased the latent period of tumor development in C3H/He and C57BL/6 mice, inhibited tumor development in BALB/c and random-bred mice, and did not affect the tumor resistance of C3HA mice. These findings might indicate a role for hereditary factors in tumorigenesis. (12 refs)

78-7008 **Development of Immunocompetence in Hamsters and the Influence of DNA Oncogenic Viruses.** (Eng) Friedman, H. (Dept. Microbiology and Immunology, Albert Einstein Medical Center, Philadelphia, PA, 19141). *Fed Proc* 37(7): 2069-2071; 1978.

The effect of simian virus 40 (SV40) and adenovirus 12 (Ad12) infection on the development of immunocompetence in hamsters was investigated. Immunocompetence to sheep RBC developed rapidly in newborn hamsters. Animals inoculated on days 2-3 after birth developed few plaque-forming cells (PFC), but inoculation on days 5-7, 10-12, and 20-40 resulted in progressively greater responses (to 35-45 x 10^3 PFC/spleen). Inoculation of hamsters with SV40 at various times during the first 40 days of life had only a slight effect on PFC response 2-3 mo later. Hamsters given SV40 during the first week of life showed a slight depression in the antibody response to sheep RBC when challenged later in life. Tumors only occurred in animals treated with SV40 during the first 2 wk of life. Maturation of the immune response to sheep RBC was impaired in hamsters inoculated at birth with SV40. Injection of Ad12 into neonatal animals had similar effects. A slight to moderate effect on immune responsiveness to *Escherichia coli* lipopolysaccharide occurred after neonatal infection with SV40 or Ad12. Max effects were noted with animals 1-2 wk old. Cell-mediated immune responses to alloantigens, mycobacteria, and tumor virus-associated antigens were assessed in normal and virus-inoculated hamsters. Inoculation of normal hamsters with BCG as early as 2 wk of age resulted in marked cellular hypersensitivity: in vivo and in vitro reactions to challenge with purified protein derivative of tuberculin (PPD) were noted. Hamsters inoculated at birth with either SV40 or Ad12 also developed sensitivity to PPD after in vivo injection of BCG, but the in vitro response was weaker. The responsiveness of hamsters to 10% saline extracts of SV40 or Ad12 tumor extracts was directly related to prior inoculation at birth with virus. Sensitization became evident around 2 wk of age, reached a max around 3-4 wk, and decreased considerably by 60-100 days. This model may be useful in examining the interactions between host immune defense mechanisms and oncogenic DNA viruses that do not directly affect lymphoid cells. (25 refs)

78-7009 **Natural Killer Cells. In Vitro and In Vivo.** (Eng) Henney, C. S. (Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104); Tracey, D.; Durdik, J. M.; Klimpel, G. *Am J Pathol* 93(2): 459-467; 1978.

Lymphoid cell populations from normal animals (rats, mice, and humans) can lyse tumor cells but not normal cells in in vitro ^{51}Cr release assays. The cells responsible for this cytotoxic activity have been characterized in the mouse and termed natural killer (NK) cells. In an attempt to discover whether NK cells are clonally distributed, they were absorbed onto monolayers of susceptible cells and then tested against other susceptible cells to see if the NK activity had been removed. The reactivity of NK cells from BCG-treated C57BL/6 mice against L5718 lymphoma cells was selectively removed by incubation of the effector cells on an L5178 cell monolayer but to a much lesser degree on a monolayer of normal DBA/2 spleen cells, which are insusceptible to NK-mediated lysis. Adsorption on the L5178 cell monolayer also removed NK reactivity against susceptible human

Chang cells. On Chang cell monolayers, NK reactivity toward both L5178 and Chang cells was totally removed by adsorption. These experiments provided no evidence for clonal distribution of NK reactivities, but they indicated that target cell susceptibility to NK action may be determined by a shared antigenic specificity. Further BCG prophylaxis assays indicate that C57BL/6 NK cells were more efficient than growth-inhibitory adherent cells in vivo in retarding EL-4 ascites tumor growth. Although preliminary, these studies show that NK cells are an important host defense against progression to a neoplastic state. (25 refs)

78-7010 **Modulation of Sensitivity to Natural Killer Cell Lysis after In Vitro Explantation of a Mouse Lymphoma.** (Eng.) Becker, S. (Dept. Obstetrics and Gynecology, Sch. Medicine, Univ. North Carolina at Chapel Hill, Chapel Hill, NC, 27514); Kiessling, R.; Lee, N.; Klein, G. *J Natl Cancer Inst* 61(6): 1495-1498; 1978.

The kinetics of modulation to increased sensitivity to natural killer (NK) cell lysis was studied in explant cultures of a YAC ascites lymphoma induced in A/Sn mice by Moloney murine leukemia virus (M-MuLV). The sensitivity of all cultures to the same CBA spleen effector population was measured in a 6-hr ^{51}Cr-release assay. The lytic sensitivity was not significantly increased after 2 hr or 1 or 5 days of culture. The sensitivity was clearly increased by 3 wk, but max sensitivity was attained only after 1-2 mo of culturing. With the more sensitive competition assay, a change in sensitivity to NK lysis could be demonstrated as early as 2-24 hr of culture. Expression of the M-MuLV-determined, cell-surface antigen, measured by quantitative absorption with intact cells, increased in parallel with NK sensitivity, whereas the H-2a alloantigen concentration decreased during in vitro culture. These findings plus those from previous work indicate that establishment of an in vitro YAC line leads to profound membrane changes in the YAC cell. These changes may condition the cell to respond with an increased NK lytic susceptibility, even if the virally determined antigenic sites by themselves are not responsible for NK lysis. (19 refs)

78-7011 **Alterations of the Antibody Response Following in Utero Exposure to Diethylstilbestrol.** (Eng) Luster, M. I. (Environmental Biology and Chemistry Branch, Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC, 27709); Faith, R. E.; McLachlan, J. A. *Bull Environ Contam Toxicol* 20(4): 433-437; 1978.

The effects of a single administration of diethylstilbestrol (DES) to mice in the prenatal period on their immune response to sheep RBC (SRBC) and *Escherichia coli* 0127 lipopolysaccharide (LPS), thymic-dependent and thymic-independent antigens, respectively, were determined. Pregnant Swiss-Webster mice were injected with DES (1.0 mg sc) on day 16 of gestation. Offspring were immunized ip with either 0.2 ml of a 10% suspension of SRBC or 0.1 ml of a 0.1-mg/m soln of *E. coli* 0127 LPS at age 7 wk. In utero exposure DES did not alter the antibody response to SRBC. LI plaque-forming cells (PFC's) were decreased in DES-treate females and signficantly increased in DES-treated males cor pared with controls. The enhanced action of DES on dire (IgM) LPS PFC in male mice could also be demonstrate during a secondary response (mice boosted with 0.01 mg LI 3 wk after the primary immunization), but antibody suppre sion was not observed in females. It is possible that exposu to DES during certain periods of fetal development stimulat or selectively programs a particular population of lympho cells, particularly those involved with T-independent antige responses, resulting in a relatively long-term alteration in th antibody response. (26 refs)

78-7012 **Surface Membrane Changes of T Cells Induce by Syngeneic Tumour Cells. I. Formation ar Uptake of Complexes of Ig and Tumour Antigens by T Cell** (Eng) Dular, U. (Dept. Medicine, Immunology, Manitob Inst. Cell Biology, Univ. Manitoba, Winnipeg, Manitob R3E 0V9, Canada); Chow, D. A.; Paraskevas, F. *Int J Cancr* 22(5): 611-620; 1978.

The formation and uptake of complexes of immunoglobuli (Ig) and tumor antigens by spleen T cells were studied in mic inoculated ip with syngeneic tumor cells (L5178Y lymph blastic leukemia and AKR thymoma). A dose of 10^7 cel from either source produced a significant increase in Ig-bea ing spleen cells 6 hr later. Incubation of normal spleen cel in serum taken 6 hr after tumor cell inoculation reproduce in vitro the changes observed in the spleen cell populatio of the serum donors, demonstrating the presence of a cyto phile Ig that was taken up by T cells. Serum collected afte tumor cell inoculation also contained Ig-antigen complexin factor (IACF) in the 4S fraction. Papain-digested tumor ce preparations, which contained specific tumor antigen activ ty, formed complexes with Ig in the presence of this facto These complexes were cytophilic for a subpopulation of cells, which thereby became Ig-positive. It is suggested tha the cytophilic Ig present in the serum 6 hr after the injectio of large numbers of tumor cells may also represent complexe of Ig and tumor antigens, the formation of which is mediate by IACF. (24 refs)

78-7013 **Surface Membrane Changes of T Cells Induce by Syngeneic Tumour Cells. II. T-Cell Defect Induced by Small Tumour Cell Inocula or Tumour Cell Anti gens.** (Eng) Chow, D. A. (Dept. Medicine and Immunology Manitoba Inst. Cell Biology, Univ. Manitoba, Winnipeg Manitoba R3E 0V9, Canada); Paraskevas, F.; Dular, U. *In J Cancer* 22(5): 621-629; 1978.

T-cell defects induced by the injection of syngeneic L5178Y lymphoblastic leukemia cells in vivo were studied using

BA/2 mice. Injection of a large number of tumor cells was lowed within 6 hr by the uptake of cytophilic immunobulin (probably complexes) by a subpopulation of T lymocytes. This "6-hr T-cell response" was abrogated when small number of tumor cells (100) small amounts of an tigen-containing preparation from tumor cells, or repeated erogenic doses of disaggregated human immunoglobulin re injected prior to the immunogenic challenge. Abrogan of the 6-hr T-cell response resulted in specific antitumor ll immunity, as measured by in vitro growth inhibition. It so resulted in loss of the enhancing effect of antibody formaon against sheep RBC that is normally detected in a B-cell cooperative system when T cells are used 6 after they have been primed with sheep RBC. It suggested that this T-cell defect may represent a echanism whereby tumor cells, in the early stages their growth, interfere with the inductive stages the immune response for a sufficient period of time allow growth of the tumor beyond immune control. (25 fs)

3-7014 **Resistance to Transplanted Cancer in Mice Increased by Live Brucella Vaccine.** (Eng) Dard, L. (Centre Regional Anticancereux, Pontchaillou. F 35 1, Rennes Cedex, France); Le Garrec, Y.; David, C.; oujas, L. *Br J Cancer* 38(3): 464-467; 1978.

he effect of a chronic state of infection on the resistance of male (C57B16 x DBA2)F_1 mice to challenge by EL4 lymhoma cells was determined. Mice were vaccinated by iv inction of 5 x 10^2 or 5 x 10^6 live *Brucella abortus*. One to 6 k later, half the animals in each group were killed; the reainder received 10^3 EL4 lymphoma cells ip. Study of the mphoid organs of the animals that were killed revealed that ter injection of the lower dose, the number of bacteria ineased until the third week. With the larger dose, however, e max number of bacteria was found as early as the first eek. In all cases, the infection subsided by 6 wk. With the wer dose, the survival of lymphoma-bearing mice was ightly but significantly increased from weeks 3 to 5. Infecon with the larger dose provoked a longer survival, particurly during weeks 1 and 2 after inoculation of the vaccine. esistance to lymphoma was better correlated with the numer of infectious organisms than with the degree of hyperasia of the liver and spleen. It is suggested that *Brucella* ay secrete a substance that inhibits cell division or that mmune mechanisms against the bacteria may also act gainst the cancer cells. (23 refs.)

8-7015 **Antigenic Content of an In Vitro Cellular Immunity Reactive Cell Surface Extract of Raji ells.** (Eng) Ng, M. H. (Medical Health Dept., Inst. Radiology Oncology, Queen Elizabeth Hosp., Kowloon, Hong Kong); Ng, W. S.; Ho, H. C. *Arch Environ Contam Toxicol* 8(3): 213-220; 1978.

The antigenic content of a Raji cell surface extract (TS) was studied by sequential absorption of rabbit antiserum to this extract with different cells. Anti-TS was reacted repeatedly with human blood cells followed by HeLa cells and human diploid fibroblasts. The residual reactivity was studied by stepwise absorption with an Epstein-Barr virus (EBV)-negative B lymphoblastoid cell line, BJAB, and then with B1-19, a clone derived from EBV-transformed BJAB cells. These processes delineated three kinds of reactivities in anti-TS having specificities for antigens on B blasts, EBV-determined cell surface antigen(s) and antigens that are exclusive to Raji cells. These results are compatible with the heterogeneous protein content of TS and with the results of earlier in vitro cell-mediated immunity studies using a similar preparation of Raji cell TS. (17 refs)

78-7016 **High Lipid Fluidity of Leukemic Cell Membranes Through Host Immune Response and Shedding of Tumor Antigen-enriched Rigid Plasma Membrane Regions.** (Eng) Van Blitterswijk, W. J. (Div. Cell Biology, Antoni van Leeuwenhoek-Huis, Netherlands Cancer Inst., Amsterdam, Netherlands); Van Der Sluis, P. J.; Hilgers, J.; Hilkmann, H. A.; Feltkamp, C. A.; Emmelot, P. *In: Advances in Comparative Leukemia Research 1977. Proceedings of the VIIIth International Symposium on Comparative Research on Leukemia and Related Diseases, held in Amsterdam, The Netherlands on 22-26 August, 1977.* Bentvelzen, P.; Hilgers, J.; Yohn, D. S., eds. (New York: Elsevier/North Holland Biomedical Press): 503 pp.; 341-344; 1978.

Thymus-derived leukemia (GRSL) in GR/A mice, maintained in ascites form by ip transplantation, possess mammary tumor virus (MTV)-induced cell-surface antigens (CSA). Seven days after transplantation, excess CSA are present in the ascites fluid in three forms: soluble, complexed, and on membrane vesicles. The microviscosity (fluidity) of phospholipids in intact cells and membrane fractions was determined by fluorescence polarization (P) using 1,6-diphenyl-1,3,5-hexatriene as a probe. Within a few transplantations in ascites form, the GRSL cells became fluid in normal nonirradiated hosts, but not in irradiated hosts. If cells from irradiated hosts were transplanted in nonirradiated hosts, the P value dropped, but the reverse did not occur to any marked degree. The increased fluidity of the cells in the ascites of normal hosts may reflect immunoselection and the shedding of CSA-enriched rigid vesicles: ie, abortive virus formation. The high fluidity of transplanted ascites GRSL cells may result in a decreased antibody-induced redistribution of antigens and a decreased sensitivity to immune killing. (7 refs)

78-7017 **Modification of In Vitro Cell Mediated Immune Responses by Protein Components of a Leukemogenic Virus.** (Eng) Fowler, A. K. (NCI, Frederick Cancer Res. Center, NIH, Frederick, MD, 21501); Twardzik, D. R.; Weislow, O. S.; Reed, C. D.; Hellman, A. *In: Advances*

in Comparative Leukemia Research 1977. Proceedings of the VIIIth International Symposium on Comparative Research on Leukemia and Related Diseases, held in Amsterdam, The Netherlands on 22-26 August, 1977. Bentvelzen, P.; Hilgers, J.; Yohn, D. S., eds. (New York: Elsevier/North Holland Biomedical Press): 503 pp.; 234; 1978.

Freeze-thaw supernatants from banded Rauscher murine leukemia virus were chromatographed and the effluent fractions were tested for lymphocyte stimulatory activity and for inhibition of lymphocyte transformation induced by mitogens. Two samples from the first peak stimulated lymphocyte transformation but had no effect on mitogen-induced transformation. Material from the second peak exerted no stimulatory or inhibitory effect. A trypsin-sensitive component of the third peak suppressed mitogen-induced transformation and lipopolysaccharide stimulation. (no refs)

78-7018 **Oncogenicity and Immunogenicity Associated with Membranes Isolated from Cell-free Ascites Fluid of Lymphoma-bearing Mice.** (Eng) Raz, A. (Basic Res. Program, NCI, Frederick, MD, 21501); Barzilai, R.; Spira, G.; Inbar, M. *Cancer Res* 38(8): 2480-2485; 1978.

The immunogenicity and oncogenicity of membranes isolated from the cell-free ascites fluid of Moloney virus-induced lymphoma (YAC lymphoma)-bearing mice were determined. The supernatant obtained after the second centrifugation of the ascites fluid was separated into two fractions by ultracentrifugation: a supernatant containing soluble membrane fragments (AFM-s) and a pellet of insoluble membrane vesicles (AFM-p). Radioimmunoassay for murine leukemia virus p30 antigen (30,000-mol wt protein) indicated that the specific activity of this antigen is 20 times higher in the AFM-p fraction than in the YAC cell homogenate. Electron microscopy of the AFM-p fraction showed that viruslike (C-type) particles were associated with the plasma membrane vesicles. In vivo experiments with strain A mice indicated that the growth of an ascites tumor is associated with two biological activities, immunity and oncogenicity, and that both are present in the cell-free ascites fluid. The two activities can be disassociated by high-speed centrifugation or UV irradiation. In all cases, oncogenicity, but not immunogenicity, was abolished by UV irradiation. The immune activity is suggested to be associated with plasma membrane vesicles that contain a high specific activity of tumor-specific surface antigens. The oncogenic activity is associated with a tumor promoter factor that increases the efficiency of either intact lymphoma cells or the C-type particles. The tumor promoter factor is associated with the insoluble membrane fraction, since all oncogenic activity was associated with AFM-p. The immune activity is associated with both the soluble and insoluble fractions, since immunity was induced by both AFM-p and AFM-s. The possibility that shedding of plasma membrane vesicles and viruslike particles is associated with the same mechanism on the lymphoma cell surface membrane is explored. (38 refs)

78-7019 **Surface Antigens in Acute Myeloblastic Leukemia: A Study Using Heteroglogous Antisera** (Eng) Tupchong, L. (Nuffield Dept. Clinical Medicine, Radcliffe Infirmary, Oxford OX2 6HE, England); MacLennan I. C. *Br J Cancer* 38(4): 481-495; 1978.

Attempts were made to confirm the presence of leukemia-specific antigens by producing rabbit antisera against human leukemic myeloblasts by a variety of techniques. Ninety-five rabbits were immunized against myeloblasts from 19 acute myeloblastic leukemia patients by techniques designed to reduce the level of antibody against normal tissue antigens. Specificities of the antisera produced were determined by a K-cell-mediated cytotoxicity test and by a noncytotoxic radioimmune anti-immunoglobulin (^{125}iodinated horse anti rabbit) binding assay. The antisera showed equal affinity to leukemic myeloblast preparations and normal splenic-lymphocyte preparations. When subsequently absorbed against pooled cadaveric human spleen cells to remove antibody against polymorphic antigens and tested against two leukemic myeloblastic preparations, 17/95 antisera had activity against at least one of the preparations. Several of the 17 absorbed sera also showed activity against phytohemagglutinin (PHA)-stimulated lymphoblasts. Although these antisera showed little activity against marrow per se, when they were absorbed twice against equal volumes of normal marrow, there was complete loss of activity against myeloblast and PHA-stimulated lymphocytes, leading to the conclusion that specificity in these antisera was directed only against normal tissue antigens. It is concluded that although these sera contained activity antigens common to leukemic myeloblasts and a minority population of normal marrow cells, they had no detectable activity against leukemia-specific antigens. (46 refs)

78-7020 **Influence of Micrococcus, BCG and Related Polysaccharides on the Proliferation of the L1210 Leukaemia.** (Eng) Verloes, R. (Laboratorium voor Chemie der Proteinen, Instituut voor Moleculaire Biologie, Paardenstraat 65; B-1640 Sint-Genesius-Rode, Belgium); Atassi, G.; Dumont, P.; Kanarek, L. *Br J Cancer* 38(5): 599-605; 1978.

The effects of *Micrococcus lysodeikticus* (ML), BCG, and a series of structurally related complement-activating polysaccharides on the nonspecific and specific immune resistance of CDF_1 mice against L1210 lymphoid leukemia were compared. The mice were vaccinated ip with 10^7 irradiated (8 kilorads) cultured leukemia cells and 1 mg BCG, ML, zymosan A, chitin, dextran sulfate, or irradiated cells alone 1 mo before ip challenge with 10^4 leukemia cells. They had increased mean survival times (MST) of 165%, 67%, 159%, 98%, 76%, and 53%, respectively, over controls. These experiments were also conducted via the iv route, but the ip route was more effective in increasing MST over controls and inducing survivors to day 90 after tumor grafting. The addition of serial booster injections of 1 mg bacteria or polysac-

arides after tumor grafting increased the MST further and duced a higher percentage of long-term survivors. Treatent before or after tumor grafting with single or multiple ses of bacteria or polysaccharides alone was not able to crease MST over control values. Furthermore, serial injecons of these complement activators + irradiated leukemia lls post-tumor grafting were also ineffective. (26 refs)

-7021 **Leukemia in AKR Mice. II. Two Modes of Suppression of In Vitro Antibody Formation by eukemic Cells.** (Eng) Roman, J. M. (Dept. Biological iences, Purdue Univ., Lafayette, IN, 47907); Golub, E. S. *ell Immunol* 40(2): 316-325; 1978.

ne in vitro suppression of the anti-sheep RBC (anti-SRBC) sponse of normal AKR mouse spleen cells by leukemic leen and thymus cells from spontaneous AKR leukemias as further investigated. Leukemic cells that suppressed only ngeneic or semiallogeneic cells were termed restricted (R), nd those that suppressed both syngeneic and allogeneic cells ere called nonrestricted (NR). The suppression mediated by leukemic cells (representing approx 80% of spontaneous mors) was overcome by the presence of irradiated allogene- cells, allogeneic supernates, or mitogens. NR suppressors, owever, exerted suppression in the presence of these subances. No differences in age, sex, or patterns of organ enrgement were observed between mice bearing R or NR tuors; in fact, individual leukemic AKR mice were sometimes en to have one lymphoid organ with R cells and another ith NR cells. The combinations of allogeneic cells used for enerating the supernates that overcame R suppression may ffer from each other in background, histocompatibility angen, or total genetic makeup. The activity of these supertes was nondialyzable and was partially sensitive to heat activation. When leukemic or normal cells were incubated supernate and then washed, normal cells were still supressable, but the leukemic cells were no longer suppressive, dicating that the supernates act on the leukemic cells rather an the normal cells. Suppression mediated by B10.A auscher murine leukemia virus-induced leukemic cells was milar to that seen in AKR leukemic cells; both required cell ntact, and 80% of the mice exhibited R suppression. This ay indicate a mode of suppression common to many lymhoid leukemias, particularly those requiring congenital or ng-term virus infection. The two types of suppression may flect a modulation of leukemic cell-surface properties or a lection of leukemic cell populations resulting from specific ost antitumor defense mechanisms. (22 refs)

8-7022 **Leukemia in AKR Mice. III. Size Distribution of Suppressor T-Cells in AKR Leukemia and eonatal Mice.** (Eng) Mulder, A. M. (Dept. Biological ciences, Purdue Univ., Lafayette, IN, 47907); Durdik, J. M.; oth, P.; Golub, E. S. *Cell Immunol* 40(2): 326-335; 1978.

The size distribution of suppressor T cells of leukemic and normal AKR mice and neonatal (C57BL/6J x DBA/2J)F_1 (BDF_1) mice was compared by velocity sedimentation. All fractions of leukemic or neonatal thymus cells suppressed the immune responses of normal cells in vitro, but all fractions of normal AKR thymus cells enhanced these responses. Spleen cells showed a different pattern of suppression. Both neonatal and leukemic spleens contained suppressor cells, but these were found only among cells sedimenting at 3.3 mm/hr or faster; ie, large cells. Cells sedimenting slower than 3.3 mm/hr neither suppressed nor enhanced the response of normal cells. In contrast, small cells in the normal spleen contained cells that enhanced the responses of normal cells. Large and small suppressor thymus cells gave similar titration curves, indicating that suppression by the small cell fraction is not due to small numbers of large cells contaminating the population and that cells in both fractions have comparable specific activity. The suppression by lymph node cells was similar to that by spleen cells: only large cells suppressed. In contrast, an sc growing lymphoma exhibited a suppression pattern similar to that of the thymus. These data are consistent with the idea that the leukemia arising in the thymus exists as both large and small cells that are able to suppress normal responses but that only the large cells are exported to lymph nodes and spleen or that both large and small cells are exported but the small cells become large cells in the peripheral organs. Both neonatal and leukemic suppression was abrogated by x-irradiation or mitomycin C treatment. Both types of suppression required cell contact. The similarities between suppressor cells in neonatal and leukemic mice may indicate that the immunological events in spontaneous leukemia of AKR mice are to some extent a replay of the early events in normal T-cell differentiation. (26 refs)

78-7023 **Protection of Newly-Hatched Chickens from Marek's Disease (JMV) by Normal Spleen Cells from Older Animals.** (Eng) Lam, K. M. (Dept. Microbiology and Immunology, Temple Univ. Sch. Medicine, Philadelphia, PA, 19140); Linna, T. J. *In: Advances in Comparative Leukemia Research 1977. Proceedings of the VIIIth International Symposium on Comparative Research on Leukemia and Related Diseases, held in Amsterdam, The Netherlands on 22-26 August, 1977.* Bentvelzen, P.; Hilgers, J.; Yohn, D. S., eds. (New York: Elsevier/North Holland Biomedical Press): 503 pp.; 111-113; 1978.

The transfer of spleen cells from intact, nonimmunized adult chickens (≥8 wk old) that are naturally resistant to JMV to newly hatched chickens protected the recipients from JMV-induced leukemia. The results of various donor treatments (thymectomy, bursectomy, cyclophosphamide, or x-radiation, or their combinations) and spleen cell treatments (to remove macrophages or T cells) showed that non-T, non-B, nonmacrophage lymphoid cells are involved in the protection. (5 refs)

78-7024 Immunoprevention of Naturally Occurring Endogenous Murine Type-C RNA Viruses. (Eng) Kende, M. (Lab. RNA Tumor Viruses, NCI, Frederick, MD, 21501); Stephenson, J. R.; Kelloff, G. J.; Al-Ghazzouli, I. K.; Dinowitz, M. *Nature* 273(5661): 383-385; 1978.

The induction of immunity to endogenous C-type viruses and the expression of these viruses were examined in BALB/c, NIH Swiss, and C57BL mice. Rauscher leukemia virus (R-MuLV) and Gross leukemia virus (G-MuLV) immunogens were injected sc on day 0 (200 μg), ip on days 14 and 28 (100 μg), and ip at 2-4 wk intervals (50 μg) for a total of 12 immunizations. All mice were killed 3 wk after the last immunization. All three strains had a virus-specific cytotoxic humoral immune response to both the R-MuLV and G-MuLV immunogens. Sera from C57BL mice were the most reactive, and sera from BALB/c were the least reactive. A predominant type-specific activity was seen with both immunogens, but a greater degree of cross-reactivity was seen with the former. At the time of killing, lymphocytes from all strains were nonreactive in cell-mediated cytotoxicity assays against the target cell used. Both immunogens induced an immunity to naturally occurring ecotropic virus in BALB/c mice: infectious ecotropic virus was detected in only 5/54 immunized animals in XC assays performed at the third passage vs 23/29 controls. At the first passage, only 3/54 animals yielded isolatable virus, and the mean titers were much less than those of controls. Both MuLV p30 and p12 expression in the spleen was closely correlated with the ability to isolate virus. Like BALB/c mice, immunized C57BL mice yielded few ecotropic virus isolates, but the incidence of isolates from control C57BL mice was lower than that from BALB/c mice. Investigations of class II and class III xenotropic virus activity at the third passage indicated that the immunized animals did not show marked reduction in endogenous xenotropic virus activity. However, the R-MuLV-immunized C57BL mice showed a trend of decreased activity in both infectivity and antigen assays that was significant with class II virus. (30 refs)

78-7025 Isolation of Leukaemia Specific Antigenic Macromolecular Moiety from Dinitrophenylated Normal Human Leukocytes. (Eng) Karande, A. A. (Cancer Res. Inst., Tata Memorial Centre, Bombay 400 012, India); Sahasrabudhe, M. B. *Indian Acad Sci Proc [B]* 87(1): 1-8; 1978.

In an attempt to isolate tumor-specific antigen from nonmalignant tissues, conformational changes were introduced in the cell-surface macromolecules of normal human WBC, and changes in the antigenicity of the cells were studied. Normal WBC suspensions were dinitrophenylated by treating them with 1-fluoro-2,4-dinitrobenzene (10^4 molecules/cell). Agglutination titers of 256 to 2,048 against leukemic cells were obtained with rabbit antiserum against the dinitrophenylated normal WBC. Affinity chromatography on an antibody-sepharose column yielded three fractions, two of which contained leukemia-specific antigenic moieties. Stron specific antileukemic agglutinating activity was obtaine when the latter two fractions were injected in an oil-in-wate emulsion into mice. The antileukemic agglutinating activit was weak when the pooled fractions were given in saline. Th antigenic fractions had mol wts of 48,000 and 21,000, respec tively. The use of the oil-in-water emulsion provided th necessary core for the antigenic proteins to orient themselve and perhaps acquire the same hydrophobic and hydrophili orientation as that seen on intact cell membranes. (27 refs

78-7026 Cell Sorter Analysis of Leukaemia-associate Antigens on Human Myeloid Precursors. (Eng Janossy, G. (Dept. Immunology, Royal Free Hosp., Pond St. London NW3, England); Francis, G. E.; Capellaro, D.; Gold stone, A. H.; Greaves, M. F. *Nature* 276(5684): 176-178 1978.

The presence of leukemia-associated antigens on human bon marrow cells was studied by separating them in a fluores cence-activated cell sorter (FACS) according to their bindin of anti-Ia-like or anti-acute lymphoblastic leukemia (ALL antibodies. After most mature granulocytic and erythroic cells were elminated, adult marrow samples containe 10%-14% cells reactive with anti-Ia serum (Ia+ cells). These Ia+ cells included larger cells, mainly myeloblasts and promyelocytes, and smaller SmIg+ (surface membrane im munoglobulin-positive) B lymphocytes. The Ia- cells were myelocytes, maturing granulocytic and erythroid cells, a few lymphocytes, and <5% myeloblasts and promyelocytes Colony and cluster-forming cells were present in both Ia+ and Ia- fractions. Clone-forming cells were found almost ex clusively among the intermediate-to-large cells, suggesting that small Ia+, ALL+ non-T, non-B cells did not form mye loid colonies. This was confirmed by staining fetal marrow cells with anti-ALL serum, separating them on the FACS and culturing them for 7 days. The ALL+ and ALL- frac tions gave, respectively, 3.2 and 626 clones per 10^4 cells These results suggest that a proportion of human myeloid precursors are Ia+ and that a few are very strongly Ia+. The results also suggest that the two Ia+ non-T, non-B cell types (the smaller ALL+ cell and the larger ALL- cell) might represent the target cells for leukemia transformation in the common (non-T, non-B) form of ALL and in acute myeloblastic leukemia, respectively. (27 refs)

78-7027 Cell-mediated Anti-tumor Response in the RL(male) 1 System. I. T Nature, Nature, H-2 DInvolvement and Antigenic Specificity of the Effector Cells. (Eng) Duprez, V. (Laboratoire d'Immunologie et de Virologie des Tumeurs, INSERM U 151, Hopital Cochin, 27, Rue du Faubourg Saint Jaques, F-75674 Paris Cedex 14, France); Gomard, E.; Levy, J. P. *Eur J Immunol* 8(9): 650-655; 1978.

he effector cells involved in the cell-mediated antitumor re-ponse in the RL male 1 lymphoma cell system were charac-rized. After in vivo priming and in vitro secondary stimula-on by radio-induced RL(male) 1 cells (RLC), syngeneic ALB/c splenic lymphocytes showed a specific but very eak cytolytic activity against target RLC. Under the same xperimental conditions, spleen cells from(B6 x BALB/c)F_1 ere at least 100-fold more efficient. In both cases the effec-or cells were cytolytic T lymphocytes (CTL), and normal -2Dantigens of the tumor cell surface were involved in the ffector-to-target cell interaction. The immune CTL were ighly specific for target RLC; of cells from 13 other trans-lantable lymphomas as well as leukemic cells from spon-neously leukemic AKR mice, only P815 mastocytoma cells owed weak cross-reactivity. The exact nature of the antigen ecognized by anti-RLC CTL remains unknown; the ematopoietic histocompatibility antigens which could have ccounted for the F_1 antiparent reaction appear irrelevant. 28 refs)

8-7028 **Increased Incidence of Spontaneous Lymphomas in Thymectomized Mice.** (Eng) Cornelis, E. A. (Section Nuclear Medicine, Dept. Diagnostic Radiology, Yale Univ. Sch. Medicine, New Haven, CT). *In: Third International Symposium on the Detection and Prevention of Cancer held by the International Study Group for the Prevention and Detection of Cancer in New York, April 26-May 1, 1976.* International Study Group for the Prevention and Detection of Cancer (New York, NY): Vol. 1(part 1): 1193 pp.; 345-351; 1977.

The influence of thymectomy on the incidence of spontaneous lymphomas was examined in (C57BL/1 x A)F_1 [(BA)F_1] mice and in (SJL/J x C57BL/1)F_1 [(SB)F_1] mice. Mice were thymectomized (Tx) within 24 hr of birth. Tx(BA)F_1 mice demonstrated impaired cellular immunity, histologic changes similar to the graft-vs-host reaction, and a markedly increased incidence of lymphomas compared with normal control mice of the same age. This difference was greatest before old age, at which time tumors became more frequent in controls. Presumptive evidence of a subcellular oncogenic agent in the tumors of Tx mice was obtained. Most tumors arising in Tx(BA)F_1 mice were rejected on transplantation into normal syngeneic controls, suggesting that the impaired cellular immunity of the Tx mice permitted the growth of tumors that were more strongly antigenic than those that occurred in normal mice. The incidence of nonlymphoid tumors was not increased in Tx(BA)F_1 mice. In (SB)F_1 mice, thymectomy was associated with a moderately increased incidence of lymphomas for a 4-mo period. Tx(SB)F_1 mice, unlike Tx(BA)F_1 mice, demonstrated no lymphoproliferative changes and no graft-vs-host like lesions. (11 refs)

78-7029 **T-Cell Lymphoma Induction by Radiation Leukemia Virus in Athymic Nude Mice.** (Eng) Ricciardi-Castagnoli, P. (Cancer Biology Res. Lab., Dept. Radiology, Stanford Univ. Medical Center, Stanford, CA, 94305); Lieberman, M.; Finn, O.; Kaplan, H. S. *J Exp Med* 148(5): 1292-1310; 1978.

Extrathymic lymphoblastic leukemias developed in 3/5 athymic nude BALB/c mice and 1/8 athymic nude NIH Swiss mice inoculated with radiation-induced leukemia virus (RadLV), and a permanent cell line (BALB/Nu_1) was established from a BALB/c lymphoma. BALB/Nu_1 was highly tumorigenic when injected ip into BALB/c and NIH/Swiss nude mice, and electron microscopy of tumor cells showed features of a typical stimulated lymphocyte and numerous C-type viral particles, designated RadLV/Nu_1 virus. Reverse transcriptase activity of this virus coincided with that of ^{3}H-labeled material in the 1.15-1.1 > g/cm^3 gradient density region. On polyacrylamide gel electrophoresis, RadLV/Nu_1 and RadLV/VL_3 viruses coelectrophoresed in most protein regions except the major envelope protein (gp71). Radioimmunoassay indicated that RadLV/Nu_1 possessed surface antigens common to or cross-reacting with the envelope antigens of RadLV/VL_3 and, to a lesser extent, xenotropic and ecotropic murine leukemia viruses. Cross-reactivity between the gp71 determinants of RadLV/Nu_1 and RadLV/VL_3 was demonstrated by membrane immunofluorescence test. RadLV/Nu_1 had thymotropic and leukemogenic activity in C57BL/Ka mice, but not in NIH/Swiss nude (nu/nu) or (nu/+). In vitro RadLV/Nu_1 was B-tropic, poorly fibrotropic, and limited to xenotropic activity. In several areas, therefore, RadLV/Nu_1 appeared to be closely similar to its parent virus RadLV. Terminal deoxynucleotidyl transferase activity in the lymphoma cells of BALB/c nude and NIH/Swiss nude mice was tenfold higher than in normal spleen cells of control nude mice. When tested for several T-cell antigens, these lymphoma cells were seen to be Thy-1.2 +, Ly-2.2 +, Ly-1.2-, and TL -. Immunoglobulin determinants were not noted. This profile resembles that of mature peripheral T cells, although the antigens were present in much lower quantities. (32 refs)

78-7030 **Atypical Lymphoid Leukemia in Ataxia Telangiectasia.** (Eng) Levitt, R. (Section Publications, Mayo Clinic, 200 First St. SW, Rochester, MN, 55901); Pierre, R. V.; White, W. L.; Siekert, R. G. *Blood* 52(5): 1003-1011; 1978.

The case reports of two sisters (23- and 25-yr-old) with ataxia telangiectasia (AT) are presented. The elder sister developed an atypical subacute lymphocytic leukemia characterized by large atypical lymphocytes and prolymphocytes, and the absence of organomegaly. Results of cytogenetic banding disclosed that both patients had identical abnormalities associated with chromosome 14 (t(14q11:14q34)) with the leukemic sister showing additional stable aberrations. The presence of the marker in the leukemic cells of the elder sister supports the theory that her leukemic cells arose from a preexisting AT lymphocyte clone. Furthermore, it is suggested that the

presence of an abnormal lymphocyte clone, depressed cellular immunity, or susceptibility to chromosomal damage or rearrangement may be responsible for the increased incidence of malignancy in AT patients and AT carriers. (37 refs)

78-7031 **Crossed Tumor Antigenicity Between the Experimental Tumors Ca M, Ca H, Ca O and Ca M_4.** (Spa) Cuadrado, S. P. (Departamento de Immunopatologia, Instituto Nacional de Oncologia, Madrid-3, Spain); Moreno Koch, M. C.; Tome Paule, C. *Rev Esp Oncol* 25(1): 45-47; 1978.

The cross antigenicity between the experimental tumors Ca M, Ca H, Ca O and Ca M_4 was studied in C_3H/he mice. Eighty animals first received a Ca M tumor transplant. After the surgical removal of this tumor, four subgroups of animals received transplants of Ca M (autograft), Ca H, Ca O or Ca M_4 tumors. Another group received a primary Ca H transplant; its two subgroups received secondary Ca H and Ca M grafts. The third group received primary Ca O transplants; the secondary transplants were Ca M and Ca O in the subgroups. The fourth group was grafted first with Ca M_4, and then Ca M and Ca M_4 were grafted in the subgroups. The immune status produced by the primary Ca M and Ca M_4 tumors offered protection against subsequent transplants of both Ca M and Ca M_4 (crossed antigenicity), but not against Ca O and Ca H transplants. The immunity produced by Ca O offered, however, protection against a subsequent Ca M transplant. The Ca H tumor failed to produce any immune protection against other tumors. The absence of crossed antigenicity between tumors in which viral particles are present suggests that these viral particles are not involved in the pathogenesis of the tumors. (no refs)

78-7032 **HLA and Glioma.** (Eng) de Moerloose, P. (Transplantation Immunology Unit, Div. Immunology and Allergy, Hopital Cantonal, 1211 Geneva 4, Switzerland); Jeannet, M.; Martin-Achard, A.; de Tribolet, N.; Seiler, R.; Guanella, N. *Tissue Antigens Histocompat Immunogenet* 12(2): 146-148; 1978.

Eighty glioma patients were typed for several histocompatibility antigens (HLA-A, -B, and -DRw), with age at time of diagnosis, sex, blood, group, and degree of malignancy being considered. Phenotypic frequencies of Bw35 and Drw1 antigens were increased in patients compared with controls, but when p values were corrected by the number of antigens tested (35), the results were not significant. (7 refs)

78-7033 **Immunotherapy of Chemically-induced Tumors in the Hamster Cheek Pouch with Dinitrochlorobenzene.** (Eng) Marshack, M. (Dept. Oral Pathology, Loyola Univ. Sch. Dentistry, Maywood, IL, 60153); Toto, P.; Kerman, R. *J Dent Res* 57(4): 625-630; 1978.

The effect of dinitrochlorobenzene (DNCB) sensitization in the buccal pouch of hamsters prior to or after the induction of cheek pouch tumors with 7,12-dimethylbenz(a)anthracene (DMBA) was studied. For tumor induction, the bucca pouches were painted with 0.5% DMBA in mineral oi 2x/wk for 14 wk. For DNCB sensitization, two pellets o cotton, each containing 1 ml of 0.1% DNCB soln, were in serted in each pouch and left to remain until expelled by th hamster (usually after 10 min). Hamsters were given tw DNCB treatments, 48 hr apart; 14 days later, the pouche were challenged with a 0.01% DNCB soln. Hamster cheel pouches treated with DMBA only developed advanced inva sive squamous cell carcinomas. Infiltration of the connectiv tissue surrounding the tumors was slight, with an av of 1 lymphocytes and < 1 plasma cell/50 μm^2. When hamster were treated with DMBA and then DNCB, benign noninva sive papillary tumors resulted. Hamsters pretreated witl DNCB followed by DMBA (starting at the same time as th challenge dose of DNCB was being responded to) develope squamous cell carcinoma in situ. However, with repeate (1-4) DNCB rechallenges, 5/16 pouches developed noninva sive papillary tumors characterized by hyperplasia with dys keratosis and 11 pouches showed no tumors. A lymphocyti and plasma cell-mediated response was seen in al DNCB-treated groups, and the lymphocyte response wa greatest (av of 50 lymphocytes/50 μm^2) in hamsters treate with DNCB following tumor induction. Lymphocytes no only invaded the lamina propria but also the epithelium These lymphocytes may be reacting to tumor-associated anti gens. (11 refs)

78-7034 **Antibody to Epstein-Barr Virus in Patients with Carcinoma of the Nasopharynx.** (Eng) Inuyama Y. (Dept. Oto-rhino-laryngology, Sch. Medicine, Keio Univ. Tokyo, Japan); Asaoka, K.; Nakajima, Y.; Horiuchi, M. Takasaki, K.; Ozu, R. *Keio J Med* 26(2): 79-89; 1977.

Antibody titers against the viral capsid antigen (VCA) of Ep stein-Barr virus (EBV) were studied in 59 patients with a malignant tumor of the nasopharynx (51 carcinomas, 8 lym phomas), 117 patients with a tumor of other sites of the heac and neck, and 263 patients without malignant disease (con trols). The geometric mean titer was 1:794 and th antibody-positive rate 82% in the patients with naso pharyngeal tumors. The corresponding values were 1:190 and 37% in patients with other head and neck tumors and 1:12(and 20% in the controls. Ridit analysis indicated that the differences among the groups were statistically significant The anti-VCA titer was determined repeatedly in patients with nasopharyngeal carcinoma. It was found that in cases of recurrence or metastasis, the titer was elevated markedly. but in patients with a short- or long-term remission, it was decreased. However, radiotherapy appeared to increase the anti-VCA titer. This could result from either antigen stimulation due to the destruction of cancer cells or the production of more antibodies by B cells following relief from the suppression of T cells. Anti-VCA titers might be useful in the

ognosis of nasopharyngeal carcinoma. The findings suggest at EBV is either carcinogenic or is a passenger virus in sopharyngeal carcinoma. (16 refs)

-7035 **Protective Effect of Thymectomy in a High Cancer Risk Population.** (Eng) Papatestas, A. (Dept. Surgery, Mount Sinai Sch. Medicine, New York, Y, 10029); Kark, A. E.; Genkins, G.; Aufses, A. H. *In: hird International Symposium on the Detection and Preven-on of Cancer held by the International Study Group for the revention and Detection of Cancer in New York, April -May 1, 1976.* International Study Group for the Preven-on and Detection of Cancer (New York, NY): Vol. 1(part : 1193 pp.; 353-365; 1977.

he cancer risk in myasthenia gravis (MG) was investigated relation to thymic pathology, the differences in cancer inci-nce between patients with and without thymectomy (Tx), d the role of Tx in altering the risk of oncogenesis. The cords of 2,000 patients registered at a New York hospital d a London hospital were reviewed; 189 of these patients d undergone Tx. A total of 149 neoplasms were found in e entire population. In women, a significant increase in lative risk (RR) was present prior to Tx both in those with nthymomatous MG and those with associated thymomas. ollowing Tx, the relative risk decreased and there was no fference from the expected numbers. In men, the RR prior Tx was also higher than that following Tx, but there were significant differences in RR. In both sexes, patients with ymomas and those with many germinal centers had a high-RR than patients without thymomas. The post-Tx de-ease in RR was more marked in patients who were operated rly after the onset of disease and in those who had reached mission. The observed numbers of neoplasms in the period fter the onset of remission were lower than expected, but in l other periods observed numbers were higher than expect-d. Thus, Tx may have a protective effect against the high ancer risk associated with thymic abnormalities. (25 refs)

8-7036 **Immunological Studies in Epidermodysplasia Verruciformis.** (Eng) Jablonska, S. (Dept. Der-atology, Warsaw Sch. Medicine, ul. Koszykowa 82a, 2-008 Warsaw, Poland); Orth, G.; Jarzabek-Chorzelska, M.; zesa, G.; Obalek, S.; Glinski, W.; Favre, M.; Croissant, O. *Bull Cancer (Paris)* 65(2): 183-190; 1978.

mmunofluorescence (IF) and cell-mediated immunity CMI) studies were made of 14 cases of Epidermodysplasia erruciformis (EV), 10 familial and 4 nonfamilial. Numerous alignancies plus one occurrence of Bowen's disease were ound in three nonfamilial cases; malignancies were also ound in three nonfamilial cases. Attempts were made to de-ermine (1) the antigenic differences of viruses inducing EV y IF; (2) the significance of CMI for progression of the isease and possible malignant transformation; (3) whether the types of human papillomavirus (HPV) inducing EV differ in their oncogenic potential; and (4) any possible correlation of the type of HPV with CMI. Two different types of HPV, HPV-3 and HPV-4, were found in the EV cases. There was a relationship between the type of HPV and the clinical picture of EV as well as the occurrence of malignant transformation. HPV-4 was more oncogenic: of the 12 cases typed, transformation occurred in 1/7 with HPV-3 and in 5/5 with HPV-4. CMI was depressed in most of the active cases and preserved in regressing and abortive cases. However, a low CMI was found in EV cases infected with HPV-3 and in persistent flat warts, also due to HPV-3, that did not undergo malignant transformation. In contrast, in a case of EV due to HPV-4, malignant transformation occurred in spite of a preserved, although lowered, CMI. HPV-1, which is responsible for plantar warts, and HPV-2, responsible for common warts, have no evident oncogenic potential. (29 refs)

78-7037 **Common Human Melanoma Membrane Antigens Detected by Mixed Hemadsorption Microassay with Serum from a Patient Undergoing Immunotherapy with Autologous Tumor Cells.** (Eng) Liao, S. K. (Ontario Cancer Foundation Hamilton Clinic, c/o Henderson General Hosp., 711 Concession St., Hamilton, Ontario, L8V 1C3, Canada); Leong, S. P.; Sutherland, C. M.; Dent, P. B.; Kwong, P. C.; Krementz, E. T. *Cancer Res* 38(12): 4395-4400; 1978.

The postimmune serum (PIS) and preimmune plasma of a patient with malignant melanoma who received 28 immunizations with autologous, irradiated, cultured melanoma cells plus BCG were tested for their reactivity in mixed hemadsorption microassays against several cell lines. No reactivity against any of the five allogeneic melanoma cell lines or five nonmelanoma lines tested was detected in the preimmune plasma, but strong reactivity against all five melanoma lines in varying titers (1:2,560 to 1:40,960) and against 2/5 nonmelanoma lines in lower titers (1:320 and 1:1,280) were found in the unabsorbed PIS. Absorption with human AB RBC, pooled peripheral blood WBC, and spleen homogenates of normal adults, did not alter this reactivity. Further absorption with cells of a human laryngeal carcinoma (KB) line reduced reactivity against the five melanoma lines 4- to 16-fold (1:160 to 1:5,120), but a strong residual common reactivity against these lines still remained. This absorbed serum no longer reacted with any of the five nonmelanoma lines. Removal of reactivity against fetal calf serum (FCS) by absorption with insolubilized FCS reduced reactivity against the melanoma cell lines to the same extent, but failed to remove reactivity against the nonmelanoma cell lines completely. Further absorption of PIS with human fetal homogenate or BCG had no effect on its reactivity against the melanoma lines. Blood group isoantigens, histocompatibility locus antigens, and FCS were ruled out as causes of the observed seropositivity against the melanoma cell lines in the final two stages of sequential absorptions. These data provide further evidence for the existence of common melanoma-associated antigens. (32 refs)

78-7038 **Genetic Control of Resistance to Tumors.** (Eng) Phillips-Quagliata, J. M. (Dept. Pathology, New York Univ. Medical Center, 550 First Ave., New York, NY, 10016); Walker, M. C. *Am J Pathol* 93(2): 487-498; 1978.

To determine whether genes mapping within the major murine histocompatibility complex (H-2) control resistance to a BALB/c plasmacytoma (MPC-11), hybrid mice from over 20 parental strains were injected sc in the right dorsal flank with 3 x 10^5 viable MPC-11 cells (a dose fatal to 100% of BALB/c controls). F_1 hybrids between BALB/c and other BALB congenic resistant (CR) strains were as susceptible to MPC-11 as homozygous BALB/c mice, which demonstrated that H-2 heterozygosity was not sufficient for resistance. F_1 hybrids between BALB/c and all but two recombinant inbred strains were resistant. In (BALB/c x B10 CR)F_1 hybrids, resistance was dependent on the presence of a single dominant autosomal gene or gene complex that segregates independently of H-2 and that has slight differential effects on various H-2 haplotypes. The resistant mice became susceptible to MPC-11 cells injected after 450 rads γ irradiation, but they remained resistant after iv silica injection. Studies of hybrids between B6 and BALB/c mice suggested that their tumor resistance was decreased by the expression of Gross viral antigens of some other viral determinant. The mechanism for this is not understood, but it might involve tolerance, suppression, or enhancing antibody. (39 refs)

78-7039 **Resonance Raman-Spectroscopic Studies of the Hapten Features Involved in the Binding of 2,4-Dinitrophenyl Haptens by the Mouse Myeloma Proteins MOPC 315 and MOPC 460.** (Eng) Kumar, K. (Dept. Chemistry, St. Mary's Univ., Halifax, N.S., Canada); Phelps, D. J.; Carey, P. R.; Young, N. M. *Biochem J* 175(2): 727-735; 1978.

The resonance Raman spectra of four dinitrophenyl (Dnp) haptens were characterized, and the binding of the haptens to mouse myeloma proteins MOPC 315 IgA and MOPC 460 IgA was studied by resonance Raman spectroscopy. The interactions between a given hapten and MOPC 315 IgA were often quite distinct from those between the same hapten and MOPC 460 IgA. More importantly, the nature of the R side chain in a Dnp-NHR compound appeared to modify the contacts between the chromophore and the protein. Thus, with the haptens studied, there was no unique set of contacts between the Dnp group and the binding site. The contacts expected between ϵ-2,4-dinitrophenyl-L-lysine and the site on MOPC 315 IgA were not detected. However, the contacts between this hapten and the site on MOPC 460 IgA were close to those predicted by a model for MOPC 315 IgA. (25 refs)

78-7040 **Symmetry of Binding Sites of a Mouse IgA Myeloma Protein (MOPC 315).** (Eng) Eisenberg, R. (Dept. Medicine, Univ. North Carolina, Chapel Hi NC, 29514); Plotz, P. *Biochemistry* 17(22): 4801-4807; 197

The mechanism of monovalency of the 7S subunit of a mou IgA myeloma protein (MOPC 315) against a large antig was investigated using affinity labels. In an equilibrium Fa assay, the subunit was shown to have only one valence f a univalent 40,000-mol wt antigen (dinitrophenyl-dextran In four experiments, an av valence of 1.1 and a Ka of 1.4 10^6 were obtained. This monovalency did not appear to b an artifact of the Farr assay used, as a small hapten (dinitr phenyl-ϵ-aminocaproic acid) tested in the same assay gave a av valence of 1.8 and a Ka of 1.4 x 10^6. Blocking binding site with a small affinity labeling hapten, bromoacetyl-dinitr phenyl-lysine, quantitatively reduced the binding of larg molecules in a manner strongly favoring the model of a sym metric 7S molecule, in which the binding of a large ligan to one site inhibits an adjacent site from binding a secon large ligand. The results of dinitrophenyl-lysine-agarose col umn chromatography strongly favored the steric hindranc model of MOPC 315 monovalency. Such a model implies tha the Fab binding sites are symmetrically arranged in the 7 subunit, but that they are too close together to permit tw large antigens to bind simultaneously. (32 refs)

78-7041 **Autoimmunity and Tumor Resistance. 3-Methylcholanthrene Tumorigenesis in New Zealand Black Mice.** (Eng) Morton, J. I. (Div. Immunology Dept. Medicine, Univ. Oregon Health Sciences Center, Portland, OR, 97201); Siegel, B. V.; Moore, R. D. *Am J Patho* 93(2): 469-485; 1978.

The susceptibility of New Zealand Black (NZB) mice to epidermal tumors induced by 3-methylcholanthrene (3-MCA) was examined as a function of age, sex, immune and autoimmune status, immunosuppressive treatment, and hepatic aryl hydrocarbon hydroxylase (AHH) levels. Results of a comparison of the frequency, type, and distribution by sex of 3-MCA-induced tumors in NZB, BALB/c, C57BL/6, and SJL/J mice given a single sc injection of 150 μg 3-MCA at age 4 mo revealed that NZB mice had a longer tumor latency period and a lower tumor incidence than the other strains. Although most of the tumors in the other groups were sarcomas, the NZB group had an almost equal number of sarcomas (21) and squamous cell carcinomas (18). In NZB mice injected with 3-MC at different ages, 4-mo-old females responded with the greatest incidence and most rapid development of tumors. Treatment with antithymocyte serum decreased the final incidence of tumors while x-irradiation with 500 rads accelerated the onset of tumors in 4-mo-old NZB mice. The development of glomerulonephritis and hematopoietic carcinomas was independent of 3-MCA injection and the presence of skin tumors. Liver AHH specific activity following ip injection of 100 mg/kg 3-MCA was highest in female NZB mice, and the activity increased gradually with age. (30 refs)

7042 **Circulating Immune Complexes in Rats Bearing Chemically Induced Tumors. I. Sequential ermination During Growth of Tumours at Various Body es.** (Eng) Hoffken, K. (Cancer Res. Campaign Lab., Univ. ttingham, Univ. Park, Nottingham NG7 2RD, England); ce, M. R.; McLaughlin, P. J.; Moore, V. E.; Baldwin, R. *Int J Cancer* 21(4): 496-504; 1978.

transplanted 3-methylcholanthrene-induced sarcoma c7) and a 4-dimethylaminoazobenzene-induced hepatoma 23) were used to determine whether the binding of cir- ating immune complexes to the complement component can be employed to monitor tumor growth in rats. Cir- ating immune complexes were measured in sequential nitoring studies in tumor-bearing WAB/Not rats. The as- employed was based on the radioimmunoprecipitation of um factors with ^{125}I-Clq or on an indirect test whereby the ibition of binding of ^{125}I-Clq to IgG aggregates by tu- r-bearer sera were measured. After an initial peak coincid- with a tumor diameter of about 0.5 cm, the Clq-binding ivity of sarcoma-bearer sera decreased until they ultimate- bound less Clq than normal rat serum. Sc implantation or growth of D23 hepatoma resulted in a change in Clq bind- by tumor-bearer serum similar to that observed with sc cula of Mc7 sarcoma. The percentage of specific inhibition tumor-bearer serum decreased at late stages of tumor wth, but it was reversed in rats whose tumors were excised ays after implantation. Antibody reactivity increased with reasing tumor burden, and the specific humoral activity s lost following resection. Following iv tumor cell injec- n, immune-complex levels increased until the terminal ges of the disease. Measurement of Clq-binding serum fac- s represents a useful method for monitoring the growth d burden of experimental animal tumors. (33 refs)

-7043 **Induction of a Tumor with Greatly Increased Metastatic Growth Potential by Injection of lls from a Low-Metastatic H-2 Heterozygous Tumor Cell ne into an H-2 Incompatible Parental Strain.** (Eng) Ker- l, R. S. (Natl. Cancer Inst. Canada Res. Group, Dept. Pa- ology, Queen's Univ., Kingston, Ontario K7L 3N6, Cana-); Twiddy, R. R.; Robertson, D. M. *Int J Cancer* 22(5): 3-594; 1978.

n H-2-heterozygous sarcoma, MDAY, originally induced 3-methylcholanthrene in an (A x DBA/2)F_1 (H-2a x H-2d; D_2F_1) hybrid was adapted for growth in the H-2-incompati- e DBA/2 parent strain by serial ip transplantation of ascites mor cells. Upon serial passage, the cells gradually lost their -2Kk antigenicity. When these H-2Kk-negative, H-2d-posi- ve variant (MDAY-D2) cells were injected sc into DBA/2 AD_2F_1 recipients, they gave rise to highly metastatic tu- ors. Widespread metastases to liver, spleen, lungs, and kid- ys were evident within 12-18 days. There was total replace- ent of liver and spleen within 2-3 wk. The tendency to etastasize and loss of the K-2Kk haplotype appeared stable d irreversible. In contrast, MDAY cells either did not metastasize or did so only to the liver in AD_2F_1 mice. The MDAY-D2 tumor originally appeared to be an H-2-loss variant tumor of an originally heterozygous tumor growing in AD_2F_1 x hosts. However, several results cast doubt on its variant nature; for example, MDAY and MDAY-D2 differed in their expression of a wide variety of cell-surface antigens and receptors. If MDAY-D2 is not a variant but is instead a newly induced DBA/2 tumor, the most likely causative agent might be an oncogenic virus harbored by the MDAY cells that is released upon cell death in vivo subsequent to an allogeneic reaction. Although its precise origin is not clear, MDAY-D2 has metastasizing properties that make it desirable for studying the biology of metastasis. (26 refs)

78-7044 **T-T Cell Collaboration in Rejection of a Syngeneic SV40-induced Sarcoma in Mice.** (Eng) Glaser, M. (Lab. Cell Biology, NCI, Bethesda, MD, 20014); Law, L. W. *Nature* 273(5661): 385-387; 1978.

The concept of T-T cell interactions during cell-mediated immune responses to tumor-associated antigens in vivo was examined. Female BALB/c mice were inoculated sc with mKSA-Tu5 tumor culture cells that had lost their oncogenic potential but had maintained tumor-specific transplantation antigen activity. Additional mice were inoculated ip with mitomycin C-treated (50 μg/ml) Meth-A cells, a methylcholanthrene-induced tumor with strong tumor-specific transplantation antigen activity. In the first experiment, various effector:target cell ratios of lymph node and thymus cells from normal BALB/c mice or mice immunized against mKSA or Meth-A cells plus mKSA or Meth-A cells were injected sc into normal BALB/c mice. No protection against mKSA cells was seen with 25:1 or lower ratios of anti-Meth-A lymph node:Meth-A cells. Thymus cells did not protect against either tumor at any cell number tested. Studies of the ability of immune lymph node and thymus cells to collaborate in the rejection of mKSA cells indicated that injection of immune lymph node or thymus cells alone did not prevent tumor growth, but together they completely inhibited tumor growth. Untreated anti-mKSA immune lymph node cells that could prevent tumor growth lost their activity after treatment with specific anti-Thy-1.2 serum and complement; this indicated that the cell type in the immune lymph nodes needed to neutralize mKSA is T-cell-dependent. Untreated immune lymph node or thymus cells at suboptimal concentrations did not neutralize mKSA when injected alone, but they did prevent tumor growth when injected together. This collaborative effect could be abrogated by pretreatment of either cell type with anti-Thy-1.2 and complement, but not complement alone, before mixing, this indicated that T cells in both lymph nodes and thymus were needed for collaboration. (12 refs)

78-7045 **Effect of Generalized Graft-Versus-Host-Reaction on B- and T-Lymphocytes and a Benzpy-**

rene-induced Murine Sarcoma. (Eng) Witting, C. (Pathologisches Institut, Westring 17, D-4400 Munster, W. Germany); Hultsch, E. *Z Krebsforsch* 92(3): 255-265; 1978.

The effects of a generalized graft-vs-host reaction (GVHR) on peripheral blood lymphocytes and benzo(a)pyrene (BP)-induced sarcomas were studied in F_1 hybrids of A/Jax female mice and BALB/c males. The GVHR was induced in 3-mo-old hybrid mice by the ip transplantation of A/Jax spleen cells (100 x 10^6). Twelve months later, BP (4 μg/g) was applied sc 1x/wk for 4 wk. Tumor incidence 12 wk after the last application was 74.5% in 200 GVHR mice, compared with 49.5% in 200 control mice. The tumors in the GVHR group were significantly larger and heavier than those in the controls, and metastases were observed in 21% of the mice vs 0% of the controls. In both groups, >95% of the tumors were myosarcomas. The percentage of T lymphocytes declined from 56%-65% in the controls to 36%-45% in the GVHR animals; the percentage of B lymphocytes increased from 21%-30% to 46%-55%. Examination of the marginal zone of the tumors revealed a marked decrease in T cells and total round cell count. There were no changes in B cells in this zone. It is concluded that the GVHR severely impairs cells, probably T lymphocytes or their subgroups, that play an essential role in tumor defense mechanisms. (26 refs)

78-7046 **Effect of Splenectomy on B- and T-Lymphocytes and a Benzpyrene-induced Murine Sarcoma.** (Eng) Witting, C. (Pathologisches Institut, Westring 17, D-4400 Munster, W. Germany); Hultsch, E. *Z Krebsforsch* 92(3): 267-274; 1978.

The effects of splenectomy (SP) on peripheral blood lymphocytes and benzo(a)pyrene (BP)-induced sarcomas were studied in female hybrids from A/Jax female mice and BALB/c males. The hybrids were splenectomized 3 wk after birth; beginning 10 wk later, the mice received three single doses of 4 μg/g BP at weekly intervals. Tumor incidence 12 wk after the last dose was 28.5% in 200 SP animals, and 49.5% in 200 BP controls. Histologically, all tumors of SP mice and 96.9% of those in control mice were myosarcomas, but the tumors were significantly smaller in the SP group. There was a significant decrease in B lymphocytes and an increase in T lymphocytes in the SP mice, compared with BP controls and untreated controls. In the marginal zone of the tumors, there was a decrease in B cells and an increase in T cells but no change in total round cell count. Studies of spleen lymphocytes in 100 untreated hybrid mice revealed a very high proportion of B lymphocytes. The antineoplastic effects of SP may have been due to the B-cell reduction, which allowed T cells to increase proportionally and thus improve host defense mechanisms. (17 refs)

78-7047 **Combined Effects of Immune Depression and Carcinogenesis.** (Eng) Trainin, N. (Dept. Cell Biology, Weizmann Inst. Science, Rehovot, Israel); Small M.; Gabizon, A. *In: Prevention and Detection of Cancer. Proceedings of the Third International Symposium on Detection and Prevention of Cancer Held by the International Study Group for the Detection and Prevention of Cancer in New York, April 26 - May 1, 1976.* International Study Group for the Detection and Prevention of Cancer. (New York, NY) Vol. 2(part 1), 2404 pp.; 1621-1630; 1978.

The influence of various lymphoid subpopulations on the behavior of transplantable tumors (a simian virus 40-induced and a methylcholanthrene-induced fibrosarcoma; the 3 LL Lewis lung carcinoma) was investigated in inbred mice. When spleen cells from tumor-bearing T mice (thymectomized, irradiated, and injected with thymocytes) were transferred with tumor cells into syngeneic recipients, the incidence of tumor metastases was increased. Spleen cells from B mice (thymectomized, irradiated, and injected with bone marrow cells) did not exhibit this activity. Thymocytes from nonsensitized animals also accelerated the growth of a primary tumor. Fractionation of the spleen cell population from tumor-bearing mice by velocity sedimentation yielded one fraction of tumor-sensitized cells that inhibited the growth of the same tumor and a second fraction that enhanced tumor growth upon transfer. These experiments suggest that subpopulations of lymphocytes with differing characteristics coexist within the spleen and that these subpopulations may exhibit opposing reactivities upon exposure to syngeneic tumor cells. Thus, immunosuppressive agents could bring about contradictory results, depending on whether the tumor-inhibiting or tumor-enhancing subpopulation is impaired. (11 refs)

78-7048 **Chemical Modification and Immunogenicity of Membrane Fractions from Mouse Tumour Cells.** (Eng) Staab, H. J. (Friedrich Miescher Laboratorium der Max Planck Gesellschaft, Spemannstrasse 37-39, 7400 Tubingen, W. Germany); Anderer, F. A. *Br J Cancer* 38(4): 496-502; 1978.

The effects of several chemicals on the immunogenicity of a crude membrane fraction isolated from mouse STU-D17 tumor cells (STU mouse embryo cells transformed by Rous sarcoma virus) were tested in syngeneic mice. Groups of 10 STU mice were immunized with membrane equivalents corresponding to 10^4, 10^2, 10^1, and 10^0 cells of modified crude membrane fractions of tumor cells or of the crude membrane fractions from DMS-modified tumor cells. A challenge dose of 10^5 viable tumor cells was given sc 14 days after immunization. Compared to 0% tumor-free control animals, immunization with unmodified membrane fraction produced 20% tumor-free animals after 90 days. Immunogenicity was appreciably elevated when the crude membrane fraction was modified by dimethyl sulfate (DMS: 50 mM) and partially elevated when modified by acetic anhydride (50 mM) or glutardialdehyde (200 mM) + [1-ethyl-3(3-dimethylaminopropyl)carbodiimide (20 mM) + methylamine (3 M)]. The membrane

ction treated with DMS produced up to 60% tumor-free mals, and the mean survival time of animals developing nors showed the greatest increase over controls. However, membrane fraction from DMS-modified tumor cells led to produce an immune response, a result that is difficult explain. For all chemical modifiers, membrane equivalents 10^3-10^4 tumor cells were most effective. Neuraminidase d no apparent effect on the immunogenicity of the tumor ls. The immunogenetic enhancement was specific, as im-unization with STU 51A/232B or fetal tissue membrane ctions, even when methylated, had no influence on tumor owth or animal survival. (21 refs)

-7049 Angioimmunoblastic Lymphadenopathy, Immunoblastic Sarcoma of B Cells. Animal Model: utoimmune-prone Inbred Armenian Hamster. (Eng) Yernian, G. (Sidney Farber Cancer Inst., 44 Binney St., Boston, MA, 02115); Gagnon, H. J.; Battaglino, A. *Am J Pathol* (1): 209-212; 1978.

n animal model of angioimmunoblastic lymphadenopathy IL) and immunoblastic sarcoma of B cells (IBS) was deveped using autoimmune-prone inbred Armenian hamsters eated with nitroso compounds. When the 16th- to 17th-genation animals were 482 days old, 25 were treated with meylnitrosourea (MNU: 70 mg/kg). Within the period 88-390 ys after treatment, 12 animals developed massive hepatolenomegaly and mesenteric lymph node tumors with or ithout Peyer's patches, pulmonary lesions, and bilateral drenal medullary hyperplasia. The 9-yr tumor-free status of e colony was interrupted when 12 untreated young adults eveloped lesions identical to those noted in the older treated imals. The characteristic presentation of the massive menteric lymph node tumors following MNU treatment sugsts that these latent B-cell lesions may be selectively respon-ve to a new and persisting antigen, with the development AIL when cells are diploid (polyclonal) and the develop-ent of IBS when cells are monoclonal. The MNU-associat-d, spontaneous Armenian hamster AIL and the transplanta-le IBS feature the characteristic triad of lesions associated ith clinical AIL, ie, the multicellularity of proliferating B ells, an extensively arborizing vasculature, and deposits of osinophilic material. (14 refs)

8-7050 Marek's Disease: Effect of Virus Pathogenicity and Genetic Susceptibility on Responses of Peripheral Blood Lymphocytes to Concanavalin-A. (Eng) Schat, . A. (Dept. Avian and Aquatic Animal Medicine, New ork State Coll. Veterinary Medicine, Cornell Univ., Ithaca, Y, 14853); Schultz, R. D.; Calnek, B. W. *In: Advances in Comparative Leukemia Research 1977. Proceedings of the VIIIth International Symposium on Comparative Research on Leukemia and Related Diseases, held in Amsterdam, The Netherlands on 22-26 August, 1977.* Bentvelzen, P.; Hilgers, J.; Yohn, D. S., eds. (New York: Elsevier/North Holland Biomedical Press): 503 pp.; 183-186; 1978.

The response of peripheral blood lymphocytes (PBL) to concanavalin A (Con A) was compared using genetic susceptibility to Marek's disease (MD) and virus pathogenicity as variables. A transient depression of the response of PBL to Con A occurred 7 days postinjection of MD-resistant N-line and MD-susceptible P-line chickens with the nononcogenic (SB-1) and oncogenic (GA-5) isolates of MD virus. A permanent depression, starting 2 wk postinjection, developed only in susceptible P-line chickens inoculated with GA-5. (7 refs)

78-7051 Lack of Correlation Between In Vivo Rejection of Syngeneic Fibrosarcomas and In Vitro Non-specific Macrophage Cytotoxicity. (Eng) Evans, R. (Dept. Tumour Immunology, Chester Beatty Res. Inst., Inst. Cancer Res., Clifton Ave, Belmont, Sutton, Surrey SM2 5PX, England); Booth, C. G.; Spencer, F. *Br J Cancer* 38(5): 583-590; 1978.

The relationship between in vitro antitumor activity and in vivo tumor rejection was studied using C57BL mice immunized against two syngeneic benzpyrene-induced fibrosarcomas (FS1 and FS6). After the mice were immunized by sc injection of 10^6 tumor cells and subsequent tumor excision, ip injections of graded doses of FS1 or FS6 cells resulted in a totally specific rejection (in terms of survival). Similarly, the peritoneal inflammatory response (in terms of cell content) was specific; on the peak days of cell production (5-7 days postchallenge) the macrophage content was approx 34%-43%. Conversely, macrophage monolayers prepared from the peritoneal exudates of immunized mice were generally nonspecifically cytotoxic, though occasional specific cytotoxocity was detected. In a 48 hr assay, peritoneal cells from immunized mice lysed ^{124}I-labeled tumor cells in a specific manner, and the loss of lytic potential after pretreatment of cells with anti-θ serum indicated that the reaction was T lymphocyte-mediated. Winn tests further showed that immune peritoneal exudate cells protected normal mice against specific tumor cells, but had no effect on unrelated tumor appearance or growth. It is concluded that the specific rejection of FS1 and FS6 was mediated by T lymphocytes, with possible assistance from macrophages. (16 refs)

78-7052 Host Genetic Factors Influencing the Occurrence of Leukemoid Reaction in BALB/cMk Mice Bearing Transplanted Tumors. (Eng) Kodama, T. (Lab. Pathology, Cancer Inst., Hokkaido Univ. Sch. Medicine, Sapporo 060, Japan); Kawamura, T.; Kobayashi, H. *Cancer Res* 38(12): 4662-4664; 1978.

Hybridization experiments involving BALB/cMk and C57BL/6 mice were carried out to study host genetic factors influencing the occurrence of the leukemoid reaction in

BALB/cMk mice bearing transplanted syngeneic fibrosarcomas. All BALB/cMk mice and all BALB/cMk x C57BL/6 F_1 ($CB6F_1$) and C57BL/6 x BALB/cMk F_1 ($B6CF_1$) hybrids, but none of the C57BL/6 mice, were tumor growth-positive (G+) and leukemoid reaction-positive (R+) after fragments of the BALB/cMk tumor CMT-6 were implanted under their back skin. Segregants that were G-,R- were found among the F_2 and C57BL/6-backcross mice. The ratio of G+,R+ to G-,R- mice was 22:8 in the F_2 mice and 14:12 in the C57BL/6- backcross progeny. Neither G+,R- mice nor G-,R+ mice were found. Mice in the parental C57BL/6, F_2, and C57BL/6-backcross groups that were G-,R- were again made tumor-bearing with the C57BL/6 BMT-3 tumor and tested for tumor growth and the leukemoid reaction. G+ mice were observed in all C57BL/6, F_2, and C57BL/6-backcross mice. No R+ mice were found. No BALB/cMk mice, but all C57BL/6 mice with BMT-3 tumor implants were G+. Neither strain with BMT-3 implants was R+. All $CB6F_1$ and $B6CF_1$ mice were G+,-R+. Segregants that were G-,R- and those that were G+,R- were found among the F_2 and BALB/cMk-backcross mice. Although the ratio of G+:G- mice was 19/7 in F_2 mice, a 12:7 R+:R- ratio was obtained in F_2 mice, seven G+,R- mice, were found. In the BALB/cMk-backcross progeny, the ratio of G+,R+ to G-,R- mice was 14:11. G+,R+ mice were observed in all BALB/cMk, F_2, and BALB/cMk-backcross mice again made tumor-bearing with CMT-6 tumors. These results, the segregation of a positive or negative leukemoid reaction in BALB/cMk mice, were in good agreement with a single dominant gene model and did not fit a two-gene interpretation. The results suggest that occurrence of the leukemoid reaction is regulated genetically in BALB/cMk mice bearing transplanted tumors. (15 refs)

78-7053 **Characteristics and In Vitro Growth Influencing Effects of the Spleen Cell Population in a Methylcholanthrene Induced Mouse Sarcoma System.** (Eng) Cornain, S. (Dept. Tumor Biology, Karolinska Institutet, S-10401, Stockholm 60, Sweden); Klein, E. *Z Immunitaetsforsch* 154(2): 101-114; 1978.

The effects of immunization on the growth of two transplantable methylcholanthrene-induced fibrosarcomas (MC57 X and MC57 Y) were studied in syngeneic C57Bl mice and their (ABY x C57Bl)F_1 hybrids. For immunization, three injections of 10^6 x-irradiated tumor cells were given sc at 10-day intervals. Ten days after the last injection, the mice were challenged sc with viable tumor cells (10^3, 10^4, 10^5, 10^6, 5 x 10^4, or 5 x 10^5 cells); 24 hr before challenge, the mice received 400 R total-body radiation. Preimmunization resulted in complete protection against tumor X, but it enhanced the growth of tumor Y. The enhancement was specific, since the effect was absent in mice pretreated with X cells. The spleens of tumor-bearing animals were enlarged, and they contained a high percentage of blasts; the proportion of complement 3 (C3)- and/or Fc-receptor cells was increased even in the T-cell enriched population. These changes were also observed to a lesser extent in the lymph nodes. The in vitro growt of tumor cells was inhibited by C3-receptor cells from th spleens of control and tumor-bearing mice and by T-cell fra tions from tumor-bearer spleens. The T cells that inhibite target cell growth were detected 14 days after tumor cha lenge; cells obtained 7 days postinoculation, ie, before tumo growth, enhanced target cell growth. The inhibitory effect c the T cells was nonspecific. The results of the in vitro test reflected only the tumor status of the host and did not relat to preimmunization. (21 refs)

78-7054 **Cooperation Between Immune T Cells and Nor mal Macrophages in the Expression of Tumo Immunity in Chickens.** (Eng) Palladino, M. A. (Dept. Pa thology, New York Univ. Sch. Medicine, 550 First Ave., Nev York, NY, 10016); Thorbecke, G. J. *In: The Macrophage an Cancer. Proceedings of the European Reticuloendothelial So ciety Symposium held in Edinburgh, September 12-14, 197* European Reticuloendothelial Society (Edinburgh, Scot land): 448 pp.; 86-96; 1977.

The possibility that the adoptive tumor-specific immunity expressed in the Winn assay by spleen cells from normal and bursectomized (Bu-x) chickens is mediated by a collaboration between immune T cells and normal recipient monocytes was investigated. Local tumor-specific immunity was transferred into 2- to 4-wk-old recipients with immune T cells from B2/B2 chickens that had rejected B2/B2 fibrosarcoma transplants with the aid of *Corynebacterium parvum*. Immunity was induced and transferred in the total absence of B cells in donors and recipients. Immunity was transferred in normal but not in irradiated or silica-pretreated recipients. Irradiated recipients were reconstituted by (1) iv injection of Bu-x spleen or bone marrow cells and (2) local addition of Bu-x spleen or purified monocytes to the tumor + immune T-cell inoculum. The induction of a delayed hypersensitivity reaction to human gamma-globulin (HGG) in a tumor cell injection site also resulted in tumor immunity. HGG immune spleen cells failed to inhibit tumor cell growth locally unless HGG was also injected in the same site. This immunity, mediated by an adoptive local delayed reaction, could also not be demonstrated in irradiated recipients and thus mimicked tumor-specific immunity in requiring cooperation between immune T cells, antigen, and macrophages. Activation of macrophages through local delayed reactions is concluded to be of paramount importance in obtaining tumor growth inhibition in Winn tests in chickens. (26 refs)

78-7055 **Reduced Spontaneous Antitumor Resistance of the Elderly Rat is Restored by *Corynebacterium parvum*.** (Eng) Keller, R. (Immunobiology Res. Group, Univ. Zurich, Schonleinstrasse 22, CH-8032 Zurich, Switzerland). *Br J Cancer* 38(4): 557-560; 1978.

The inoculation of DA rats with *Corynebacterium parvum*

creased the in vivo resistance of rats (in terms of survival) ed 30 days or 3-4, 12, or 16-18 mo to the later inoculation 7,12-dimethylbenzanthracene (DMBA)-induced fibrosarma ascites tumor cells. The survival of rats inoculated with ^{3} syngeneic DMBA-induced tumor cells alone decreased th age and was independent of body wt. However, when e rats were inoculated ip with 3 mg heat-killed strain 2683 *parvum* 1 wk before tumor challenge, local tumor resistce was increased similarly in rats aged 30 days and 3-4 mo; both age groups, *C. parvum* treatment was well-supported d survival time after tumor cell injection was prolonged gnificantly. Pretreatment with *C. parvum* was much more xic for rats aged 12 and 16-18 mo and caused the loss of %-30% of these animals within 10 days. In the survivors, sistance to tumor challenge varied. In 5/6 experiments, the etreatment caused a distinct enhancement of local tumor sistance that was sometimes more pronounced than that in unger animals; in one experiment, only minor simulatory fects were noted. (30 refs)

8-7056 **In Vivo Anti-tumour Activity of *C. parvum* Stimulated Peritoneal Exudate Cells.** (Eng) IcBride, W. H. (Dept. Bacteriology, Univ. Edinburgh Medil Sch., Edinburgh, Scotland); Peters, L. J.; Mason, K. A.; arrow, G.; Milas, L. *In: The Macrophage and Cancer. Proeedings of the European Reticuloendothelial Society Symposim held in Edinburgh, September 12-14, 1977.* European eticuloendothelial Society (Edinburgh, Scotland): 448 pp.; 73-181; 1977.

he antitumor activity of *Corynebacterium parvum*-stimulatd peritoneal exudate cells (CP-PEC) was investigated in 3Hf/Bu/E mice in a Winn-type sc transfer assay. The cells hibited tumor growth when they were admixed with 10^3 or 0^4 fibrosarcoma cells (Fsa) and injected into the mice. When ie ratio of CP-PEC:Fsa was 10:1 or higher, there was a gnificant delay before tumors were detected and a lower nal incidence of tumor takes. Normal cells or plastic icrospheres interfered with the action of the CP-EC, presumably by interposing themselves between ie target and effector cells. In other experiments, ice were inoculated with 4×10^5 Fsa sc and with three oses of CP ip. There was little activity in the PEC om normal tumor-bearing mice not treated with P. In contrast, the level of activity in PEC from CP treated ormal and tumor-bearing mice was considerable, even at an ffector:target cell ratio of 2.5:1. This activity level was maintined in the tumor bearers for some time after injection of P, but it declined in the normal mice. This suggests that iere is some interplay between the stimulus provided by the umor and that provided by CP, possibly involving a specifially immune T-cell population. There was an unexpected bservation of depressed reactivity in the splenic T-cell pool om CP-treated tumor bearers, a finding that contrasts with he enhanced activity of splenic T cells upon iv transfer. This onflict may be due to the different abilities of T-cell subsets o migrate to the tumor site. (19 refs)

78-7057 **A Study on Cells Participating in the Antitumour Effect of *Corynebacterium Parvum*.** (Eng) Stiffel, C. (Dept. Immunogenetics (U 125 INSERM and ER 70 CNRS), Fondation Curie, Institut du Radium, 26 rue D'Ulm, 75 231 Paris Cedex 05, France); Mazurek, C.; Chalvet, H.; Biozzi, G. *In: The Macrophage and Cancer. Proceedings of the European Reticuloendothelial Society Symposium held in Edinburgh, September 12-14, 1977.* European Reticuloendothelial Society (Edinburgh, Scotland): 448 pp.; 164-172; 1977.

The effects of x-rays and silica on the activity of *Corynebacterium parvum* were studied in two quantitative systems: (1) phagocytosis and antibody synthesis in C3H mice and (2) mortality induced by a transplantable syngeneic mammary carcinoma. Ip injections of 5 mg silica (a specific macrophage toxin) or 500 rads whole-body irradiation inhibited *C. parvum*-induced stimulation of the phagocytic activity of liver and spleen macrophages when given two days before, but not two days after, *C. parvum* administration. The same irradiation dose totally abolished the antibody response to 10^8 sheep red blood cells (SRBC) injected 3 or 10 days later, but partial antibody synthesis occurred when the antigen was injected 20 days after irradiation and agglutination titers were normal in mice immunized at 40 days. Silica had no effect on the antibody response to SRBC or on the adjuvant effect that *C. parvum* supplied to the reaction. Silica injected 2 days before or 4 days after *C. parvum* abolished the bacteria's normal antitumor effect (ie, survival) against the transplanted mammary carcinoma. Irradiation also abolished this effect when administered 3 or 10 days before to *C.parvum*. The antitumor activity of *C.parvum* was restored totally when it was injected 40 days after irradiation. Both silica and x-rays had a similar effect on *C.parvum* antitumor capabilities and macrophage phagocytosis, but only x-rays inhibited antibody synthesis in response to SRBC. (19 refs)

78-7058 **Tumor-directed Antibodies in Cancer: A Study of Immune Complexes Eluted from Kidneys of Humans and Experimental Animals with Malignancies.** (Eng) Slovin, S. F. (Columbia Univ., New York, NY, 10027). *Diss Abstr Int B* 39(4): 1700-1701; 1978. (no refs)

78-7059 **Reduction of Respiratory Tract Binding of Benzo(a)pyrene in Mice by Immunization.** (Eng) Moolten, F. (Dept. Microbiology, Boston Univ. Sch. Medicine, Boston, MA, 02118); Capparell, N.; Boger, E. *J Natl Cancer Inst* 61(5): 1347-1349; 1978.

The feasibility of immunizing the respiratory tracts of mice with 5-fluoro-12-methylbenzanthryl-7-acetic acid (FMBAAA)-bovine serum albumin (BSA) conjugates was investigated. Male inbred A/J mice were immunized ip with the FMBAAA-BSA conjugate (0.2 mg antigen) in two doses 2 wk apart. Intranasal immunization (30 μg antigen in 5 ml

buffer soln was pipetted onto each nostril) was begun 1 wk after the second ip injection and continued 3x/wk for six instillations. Five days after the last dose of antigen, each mouse received two instillations of benzo(a)pyrene (BP) in each nostril 2 hr apart [total dose 92 nanograms (ng)]. The mice were killed 20 hr later, and BP was measured in the nose and tracheal tissues. Total BP bound to these respiratory tissues was 0.0334 ng in animals that received FMBAAA-BSA conjugate, 0.0502 ng in unimmunized mice, 0.0527 ng in BSA-treated mice, and 0.0507 ng in mice treated with an unconjugated mixture of FMBAAA and BSA. γ-Globulin fractions eluted from tracheas of immunized, but not unimmunized, mice exhibited significant BP-binding capacity, indicating that the reduction of bound BP in immunized mice was caused by the interception of BP by antibodies in respiratory secretions. The one-third reduction of BP in the respiratory tracts of the FMBAAA-BSA-immunized mice given 92 ng of BP is equivalent to a reduction in exposure of 30 ng. The data suggest the potential capacity of respiratory tract immunization to cope with significant human exposures to BP and other polycyclic aromatic hydrocarbon carcinogens. (5 refs)

78-7060 **Gamma Heavy Chain Disease in Man: Translation and Partial Purification of mRNA Coding for the Deleted Protein.** (Eng) Alexander, A. (Dept. Biochemical Sciences, Princeton Univ., Princeton, NJ, 08540); Barritault, D.; Buxbaum, J. *Proc Natl Acad Sci USA* 75(10): 4774-4778; 1978.

Long-term-cultured lymphoid cells from a patient with heavy chain disease continue to produce a protein antigenically identical to the deleted heavy chain disease protein found in the patient's serum. The size of the messenger RNA (mRNA) coding for this protein was determined, and evidence for the presence or absence of translatable light (L)-chain mRNA was sought. The primary in vitro translation product was 1,500-2,000 daltons larger than the polypeptide portion of the cytoplasmic or secreted protein. Methionine was present at the amino terminus of the translation product. The mRNA sedimented at 15.5S on sucrose gradients and, therefore, appears to be smaller than the 17S mRNA coding for normal-sized mouse γ chains. It contained a base sequence that coded for a hydrophobic amino-terminal peptide not found in the cytoplasmic protein. There was no evidence for the synthesis of translatable L-chain mRNA by these cells. The data suggest that the protein resulted from a primary somatic genetic event that gave rise to a cell product bearing a normal aminoterminus sensitive to limited proteolytic digestion. The serum protein thus appears to begin in the hinge region but, in fact, contains a normal heavy chain initiation site. (28 refs)

78-7061 **Cancer Related to Asbestos Exposure: Immunological Studies of Patients at Risk.** (Eng) Kagan, E. (Dept. Immunology, Natl. Res. Inst. Occupatio Diseases, South African Medical Res. Council, Johann burg, S. Africa); Solomon, A.; Cochrane, J. C.; Beissner, I.; Gluckman, J.; Kuba, P.; Webster, I. *In: Prevention Detection of Cancer. Proceedings of the Third Internatio Symposium on Detection and Prevention of Cancer Held the International Study Group for the Detection and Prev tion of Cancer in New York, April 26 - May 1, 1976.* Inter tional Study Group for the Detection and Prevention of C cer. (New York, NY): Vol. 2(part 1), 2404 pp.; 1631-16 1978.

Several immunological parameters were evaluated in t groups of asbestos-exposed patients who were at possible r of developing asbestos-related cancer. Group 1 consisted 20 patients with asbestos-related pleural thickening; Gro 2 consisted of 26 patients with parenchymal asbestosis. Co paratively minor immunological abnormalities were not among Group 1 patients, and they were generally restrict to isolated disturbances of humoral immunity. All cont subjects and all except 2 Group 1 patients exhibited stro cutaneous delayed hypersensitivity reactions to 2,4-dinitr chlorobenzene (DNCB), but 17/26 Group 2 patients ma fested cutaneous anergy, indicating defective expression cell-mediated immunity. In vitro assays also showed sign cantly impaired cellular immunity in Group 2. Levels secretory IgA and serum concentrations of IgA, IgG, Ig and IgE were significantly increased in Group 2, but ser IgA and IgG levels were significantly reduced in Group The percentage and absolute numbers of T lymphocytes we significantly lower in Group 2 compared with contro Cold-reactive serum lymphocytotoxins were detected in 55 of Group 1 and 81% of Group 2 patients vs 22% of contro These antibodies showed autoreactivity in 25% of bo groups vs 7% of controls. The imbalance between cellu and humoral immunity seen in these patients may be a ma festation of abnormal T-cell/B-cell interaction and may ha relevance to the possible causal role of asbestos in the indu tion of malignancy. (28 refs)

78-7062 **Early Increase of Serum Alpha-Fetoprotein Spontaneous Hepatocarcinogenesis in Mi** (Eng) Jalanko, H. (Dept. Serology and Bacteriology, Un Helsinki, 00290 Helsinki 29, Finland); Virtanen, I.; Engva E.; Ruoslahti, E. *Int J Cancer* 21(4): 453-459; 1978.

The concentration of serum alpha-fetoprotein (AFP) was f lowed by competitive double antibody radioimmunoassay C3H mice having a high incidence of spontaneous hepatoc lular carcinoma. No general elevation of serum AFP le with age was seen in mice without tumors. With a sing exception, mice bearing hepatocellular carcinomas had i creased serum AFP levels. In some mice this increase f lowed a biphasic course. Mice killed within 1 mo of the tir when an elevation of serum AFP was first observed had sm tumors or no detectable tumor. Premalignant lesions we present in the livers of 11/16 mice that had elevated AFP b

ancer, but only 1/14 mice with normal AFP had such ations. Autologous antibodies to AFP were produced in oup of C3H mice by immunization with rat AFP. These AFP antibodies reduced the amount of serum AFP but no effect on the incidence of spontaneous hepatomas. The lts suggest that spontaneous hepatocarcinogenesis pro- s through almost the same premalignant lesions as nically induced carcinogenesis and that an increase in production occurs early during this process, often eding macroscopic lesions. Repeated testing for AFP in viduals at risk of developing liver cancer might reveal ors at a curable stage. (24 refs)

063 **A Microassay for the Detection of Tumour-specific Complement-dependent Serum otoxicity Against a Chemically Induced Rat Hepatoma.** g) Price, M. R. (Cancer Res. Campaign Labs., Univ. Notham, University Park, Nottingham NG7 2RD, England). *nsplantation* 25(4): 224-226; 1978.

nort-term ^{51}Cr-release microassay was developed for the ction of tumor-specific complement-dependent serum toxicity against a transplanted 4-dimethylaminoazoben- -induced rat hepatoma (D23). The method involves the ential sampling of supernatants in the wells of microtiter es containing serum (100 μl), hepatoma cells (10^4 cells 0 μl), and guinea pig serum (100 μl) as complement. In presentative test, the complement-dependent cytotoxicity epatoma D23-bearer serum and normal rat control serum determined after 2-, 4-, and 8-hr incubations. The comnent-dependent cytotoxicity of tumor bearer serum was ent at the three time intervals, even at dilutions of 1/80 r 4 hr of incubation. Using this assay, the serum from rats ring ip grafts of hepatoma D23 exhibited tumor-specific plement-dependent cytotoxicity for hepatoma D23 cells. um from rats bearing sc tumor grafts also exhibited tu- -specific complement-dependent cytotoxicity, in contrast revious reports. Attempts to use rabbit serum as a source omplement met with variable success. The application of technique economizes on the time, labor, and reagents uired to perform the test in individual plates. (11 refs)

7064 **Circulating Immune Complexes in Rats Bearing Chemically Induced Tumours. II. Characterization of Sera from Different Stages of Tumour Growth.** (Eng) ffken, K. (West Deutsches Tumorzentrum, Innere Unisitatsklinik, Hufelandstrasse 55, D-4300 Essen 1, W. Gerny); Price, M. R.; Moore, V. E.; Baldwin, R. W. *Int J ncer* 22(5): 576-582; 1978.

a of WAB/Not rats bearing ip implants of a 4-dimelaminoazobenzene-induced hepatoma were fractionated by Sephadex G200 and diethylaminoethylcellulose ion-exchange column chromatography and then examined for their capacity to bind radioiodinated complement C1q to immune complexes, to bind soluble tumor-specific antigen, and to react with antigens on the surface of hepatoma cells. Sera were obtained from rats bearing implants for 3 and 9 days, since these samples display significantly higher and lower capacities, respectively, to bind C1q compared with normal rat serum. Immune complexes were present at both early and late stages of tumor growth; however, inherent limitations in the C1q test prevented their detection in unfractionated sera from late tumor bearers. Fractionated sera from early and late tumor-growth stages displayed significantly greater C1q-binding activity than corresponding normal rat serum fractions in the region 7S-19S, but in unfractionated sera, only samples from rats at early tumor stages exhibited this activity. The results suggest that the detection of immune complexes in unfractionated late tumor-bearer serum by ^{125}I-C1q fixation is masked by the presence of excess tumor-specific antibodies and by a shift from complement-fixing to noncomplement-fixing antibodies. (25 refs)

78-7065 **Compared Humoral and Cellular Immune Response to Herpes Simplex (HSV-2) Antigens in Women with Cervical Carcinoma.** (Eng) Thiry, L. (Institut Pasteur du Brabant, Brussels, Belgium); Sprecher-Goldberger, S.; Hannecart-Pokorni, E.; Gould, I.; Bossens, M. *In: Third International Symposium on the Detection and Prevention of Cancer held by the International Study Group for the Prevention and Detection of Cancer in New York, April 26-May 1, 1976.* International Study Group for the Prevention and Detection of Cancer (New York, NY): Vol. 1(part 1): 1193 pp.; 231-243; 1977.

The specific immune status of patients with cervical dysplasia and cervical carcinoma was characterized by determining their specific humoral and cell-mediated responses and comparing the results with those of a control group. The test subjects comprised (1) 30 with a normal cervix, (2) 33 with dysplasia, (3) 32 with cervical carcinoma, (4) 11 cancer patients undergoing radiation therapy, and (5) 35 patients that had been treated (24, surgically). Neutralizing antibodies (ab) to herpes simplex virus type 2 (HSV-2) were studied by neutralization kinetics before and after adsorption of serum samples with Staphylococcus Cowan A. Ab remaining in the supernatant were non-IgG ab. These ab were found in 6%, 42,%, 66%, 27%, and 6% of the respective five groups. Heparinized blood was obtained from most of these patients. Thymidine incorporation into washed nonpurified lymphocytes was studied in the presence of killed HSV-2 and HSV-1, as well as in the presence of mitomycin C-treated hamster cells transformed by HSV-2 or simian virus 40 or nontransformed cells. Specific stimulation by the HSV-2-transformed cells was obtained in 0%, 24%, 36%, 82%, and 11% of the five groups. Differences among the various groups were less clear-cut when HSV-2 virions were

used as antigens to stimulate the lymphocytes (24%, 37%, 45%, 40%, and 10%, respectively, had lymphocytes responding to the virions). The lymphocyte responses were rarely associated with the non-IgG ab. Some in vivo mechanism must modulate the immune reactions in such a way that the simultaneous presence of non-IgG ab to HSV-2 and lymphocyte responsiveness to this virus is excluded. There was also a negative correlation between the humoral and cell-mediated responses. (16 refs)

78-7066 **Carcino-embryonic Antigen (CEA) and Alpha-Fetoprotein (AFP) in Cancer-prone Families.** (Eng) Guirgis, H. (Creighton Univ., Omaha, NB); Lynch, H.; Keller, R.; Tomasi, T.; Vandervoorde, J.; Lynch, J.; Rankin, L.; Maloney, K.; Harris, R. *In: Prevention and Detection of Cancer. Proceedings of the Third International Symposium on Detection and Prevention of Cancer Held by the International Study Group for the Detection and Prevention of Cancer in New York, April 26 - May 1, 1976.* International Study Group for the Detection and Prevention of Cancer. (New York, NY): Vol. 2(part 1), 2404 pp.; 1563-1571; 1978.

Carcinoembryonic antigen (CEA) and/or α-fetoprotein (AFP) levels were measured in 698 individuals (521 relatives and 177 spouses) from 11 cancer-prone families. CEA was determined by the Hansen method and AFP by a fluorescence technique. The families were divided into the following categories: (1) breast cancer kindreds (6 families); (2) cancer family syndrome (CFS) kindreds (3 families); (3) malignant melanoma kindred (1 family); and (4) Hodgkin's disease kindred (1 family). Individuals were classified as smokers or nonsmokers. Mean plasma CEA titers/family were 1.11-3.08 ng/ml with standard deviations in the range 0.46-9.13 ng/ml. There were significant intrafamily variations and even greater interfamily variations. Significant elevations of CEA were detected in the spouses of CFS relatives and in nonsmoking spouses of patients from breast cancer-prone families. In the two families tested for AFP, 50% of the individuals were positive for AFP on their lymphocytes. No correlation was found between elevated plasma CEA titers and the AFP test, but there was a significant correlation between a positive AFP test and the suppression of stimulated lymphocytes by the patient's sera. The significance of these results remains to be determined. (17 refs)

78-7067 **Incidence of Spontaneous Tumours in Neonatally Thymectomized Rats.** (Eng) Dawson, P. J. (Dept. Pathology, Univ. Chicago, Chicago, IL, 60637); Fieldsteel, A. H.; McCusker, J. *Br J Cancer* 38(3): 476-478; 1978.

The spontaneous tumor incidence in neonatally thymectomized (Thy-x) Wistar/Lewis and Buffalo rats was compared with that in intact rats. In addition, 214/1,007 Thy-x Wistar/Lewis rats also were treated with antithymocyte serum (ATS) and/or 250-450 rads of whole-body x-radiation. The most common ATS dose used was 0.5-2.4 ml ip weekly for 3-6 mo beginning at 2-3 mo of age. A total of 33/51 Thy-x Buffalo rats also were irradiated, and 16 of these were given 0.5 ml ATS ip weekly for 6 mo beginning at 2-7 mo of age. Three intact Buffalo and five intact Wistar/Lewis rats received 0.5 ml ATS weekly for 3 mo beginning at 2-7 mo of age. Buffalo rats (24) also were irradiated after they were inoculated with *Mycobacterium leprae* into the foot pads. Tumors were noted in 1/23 male and 10/28 female Thy-x and 2/4 male and 17/32 female intact Buffalo rats. For Wistar rats, the respective figures were 43/517 and 66/490 for the Thy-x animals and 4/65 and 6/43 for intact animals. Breast tumors were the most common tumors, followed by leukemia and fibrosarcomas. It was concluded that the incidence of spontaneous tumors in the two strains was not influenced by prolonged immunosuppression. (11 refs.)

78-7068 **Immune Response of Prostatic Cancer Patients to Cytomegalovirus-infected and -transformed Human Cells.** (Eng) Laychock, A. M. (Milton S. Hershey Medical Center, Pennsylvania State Univ. Coll. Medicine, Hershey, PA); Gedér, L.; Sanford, E. J.; Rapp, F. *Cancer* 42(4): 1766-1771; 1978.

The possiblility of a relationship between cytomegalovirus (CMV) infection and prostatic cancer was investigated. The indirect immunofluorescence (IF) test was used to determine the prevalence of humoral immunity to CMV-induced antigens in 35 patients with prostate cancer, 22 with benign prostatic hyperplasia, 17 with transitional cell carcinoma (TCC) of the bladder, and 18 nonurogenital cancer controls. Sera from the four groups were screened for antibodies to the CMV-transformed cells CMV-Mj-HEL-2 and CMV-Mj-HEL-2,T-1. A high percentage of sera from all test groups reacted when tested against fixed and unfixed preparations of CMV-Mj-HEL-2,T-1 cells at passages 46 and 56, respectively. There were no major differences among the groups when the sera were tested against unfixed cells. With fixed cell preparations, approx 80% of serum specimens from prostatic cancer and bladder cancer patients demonstrated fluorescence. In IF tests against cells infected with strain CMV-Mj, the prostatic cancer group had the fewest patients with titers $< 1{:}4$ (3%) but the most patients with titers $\geq 1{:}64$ (66%). Sixty-five percent of the patients with TCC also possessed antibody titers $\geq 1{:}64$. Thirty-two percent of the patients with benign hyperplasia had antibody titers $\leq 1{:}4$, and only 32% reacted with CMV-Mj-infected cells in serum dilutions $\geq 1{:}64$. In the controls, 39% had titers $< 1{:}4$, 44% had titers between 1:4 and 1:64, and only 22% had titers $\geq 1{:}64$. A significantly higher number of prostatic cancer patients reacted with the CMV-Mj-infected cells at a serum dilution

:4 or higher than did patients with benign hyperplasia or controls. There was no significant difference in reactivity veen the prostatic cancer patients and the TCC patients, ough a higher ratio of the prostatic cancer group had V-Mj antibodies. When screened against CMV-trans-ned human cell lines, the reactivity of the sera followed rate of expression of CMV-related antigens of cell lines l in these tests. The data enhance the possibility of finding etiologic association between CMV and prostatic cancer. refs)

See also:
*(Rev.): 78-6671, 78-6681, 78-6682, 78-6684, 78-6687, 78-6688, 78-6689, 78-6690, 78-6691, 78-6692, 78-6693, 78-6694, 78-6695.
*(Chem.): 78-6735, 78-6736, 78-6782.
*(Viral): 78-6860, 78-6871, 78-6875, 78-6879, 78-6883, 78-6884, 78-6890, 78-6909, 78-6911, 78-6919, 78-6929, 78-6939, 78-6956.
*(Path.): 78-7071, 78-7101, 78-7110, 78-7136.
*(Epid.-Biom.): 78-7165, 78-7169.

78-7069 Chromosomal Evidence for the Transplantability of the Shay Chloroleukemia. (Eng) Derelanko, M. J. (Dept. Biology, 952 Brown Bldg., Washington Sq., New York, NY, 10003); Moorthy, A. S.; LoBue, J.; Meagher, R. C.; Gordon, A. S.; Mitra, J.; Fredrickson, T. N. *J Surg Oncol* 10(5): 441-445; 1978.

Female Long-Evans rats were injected iv with Shay chloroleukemia (SCL) cells, and the resulting tumor cells were studied to determine whether or not SCL is a true transplantable leukemia resulting from colonization of donor leukemic cells. During blast crisis in the recipient rats, the leukemic blast cells were mitotically active in the peripheral circulation, and a large number of mitotic figures were found. Karyotype analyses of the SCL tumor cells used to induce the leukemia demonstrated the presence of X and Y chromosomes. Similarly, all 180 metaphase figures of leukemic blast cells from the peripheral circulation of female rats inoculated with SCL showed the X and Y chromosomes. The data demonstrate that transmission of SCL is a result of donor cell colonization and that SCL can be considered a true transplantable leukemia. Viruses described in SCL by other workers are probably not involved in the transmission of this leukemia. (20 refs)

78-7070 Chromosomes and Causation of Human Cancer and Leukemia: XXVIII. Value of Detailed Chromosome Studies on Large Numbers of Cells in CML. (Eng) Sonta, S. (Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263); Sandberg, A. A. *Am J Hematol* 3: 121-126; 1977.

Bone marrow aspirates, peripheral blood, and, in one case, splenic tissue from six patients with Philadelphia chromosome (Ph^1)-positive chronic myelocytic leukemia (CML) were subjected to chromosomal analyses. Clones with additional chromosome abnormalities (besides a Ph^1 and a missing Y chromosome) were shown to exist in the uncomplicated, chronic phase of CML when a large number of cells (110 to 500) was examined. These abnormalities were not evident during routine cytogenetic study (10 to 50 cells). The abnormalities were an extra Ph^1 chromosome, missing chromosomes 16 and 17, an isochromosome of the long arm of No. 17, and an abnormal chromosome 2. In 5/6 cases, aneuploid clones observed during the examination of 110 to 500 cells during the chronic phase became the dominant ones during the blastic phase. The data indicate that in some cases of CML, a variety of karyotypically abnormal cells is already present in the marrow during the chronic phase and that the quantitative shift in favor of these abnormal cells as a result of their increased proliferative capacity constitutes the chromosomal aspects of the blastic phase, rather than the de novo genesis of cells with chromosome changes previously not seen in the marrow. (8 refs.)

78-7071 An Autopsy Case of Acute Myeloblastic Leukemia with Persistent High Anti-EBV-antibody Titer. (Jpn) Musashi, M. (Third Dept. Internal Medicine Hokkaido Univ. Sch. Medicine, Hokkaido, Japan); Maekawa, I.; Sakurada, K.; Fujimoto, N.; Noguchi, H.; Shiraishi, T. *Jpn J Clin Hematol* 19(8): 1079-1085; 1978.

A case of acute myeloblastic leukemia (AML) with persistent high anti-Epstein Barr virus (EBV)-antibody titer is presented. A 62-yr-old woman presented with fatigue, palpitation, and shortness of breath. Physical examination revealed anemia, but there was no hepatosplenomegaly or superficial lymphadenopathy. Examination of peripheral blood showed moderate anemia, thrombocytopenia, and no atypical cells. However, 4.5% of atypical cells were observed in a bone-marrow specimen; these cells were positive for peroxidase activity and Sudan Black B stain and nucleolus staining showed M-type cells. These results prompted the diagnosis of AML. Chromosome study of the marrow cells revealed karyotype (46xx, 5q-). Two mo later, a tumor was found at the middle nasal meatus that proved to be a well-differentiated hemangioma. Examination of the patient's anti-EBV titer revealed a titer of 1:1280 for antibody to viral capsid antigen (anti-VCA) of 1:80 for antibody to erythrocyte antigen (anti-EA). Anti-VCA and anti-EA persisted at high levels (1:640 and 1:320, respectively) throughout the clinical course. After the appearance of the nasal tumor, the number of leukemic cells increased in the peripheral blood and bone marrow, and a marked hepatosplenomegaly developed. Autopsy revealed leukemic cell proliferation and infiltration in the bone marrow, liver, and spleen. The occurrence of AML with high anti-EBV is rare, and the relationship between AML and EBV infection found in the present case is discussed. (27 refs)

78-7072 Leukemia in Radiation-treated Patients: Cytogenetic Studies in Eight Cases. (Eng) Goh, K. (Medical Oncology-Hematology Unit, Monroe Community Hosp., Rochester, NY, 14603); Bauman, A.; Bakemeier, R.; Lee, H.; Woll, J. E. *Am J Med Sci* 276(2): 189-195; 1978.

The case reports and cytogenetic studies are presented of eight patients (6 women, 2 men; age range 17-66 yr) who developed leukemia several years after diagnosis and treatment for an unrelated primary malignancy. These patients originally had a multiple myeloma, a Wilms' tumor, Hodg-

's disease, a seminoma, a breast cancer, or lymphomas (3 es). All patients received extensive radiation therapy 00-18,329 rads); two were also treated with nitrogen mus- l and one each with chlorambucil, cyclophosphamide, and nomycin D. Cytogenetic studies were performed on all ients by direct methods; and chromosome abnormalities e seen in every patient. Only 42% of the karyotyped meta- ses were diploid, and it was quite common to find less n the full diploid complement of chromosomes. The most sistent abnormal chromosomes, present in 91/516 meta- ses analyzed, was a small G chromosome replacing the mal G. Other chromosome abnormalities included ring omosomes, large acrocentric chromosomes, submetacen- chromosomes, pulverized chromosomes, pseudodiploid taphases, and chromosome breaks. It is suggested that in se patients there was a causal relationship between previ- radiation treatment and subsequent development of leu- nia. (19 refs)

-7073 **Lymphoblastoid Cell Lines from Patients with Chronic Lymphocytic Leukemia: Identification Tumor Origin by Idiotypic Analysis.** (Eng) Hurley, J. N. ockefeller Univ., New York, NY, 10021); Fu, S. M.; Kun- , H. G.; McKenna, G.; Scharff, M. D. *Proc Natl Acad Sci A* 75(11): 5706-5710; 1978.

arge number of continuous lymphoblastoid cell lines were ived from the peripheral blood mononuclear cells of two nale chronic lymphocytic leukemia patients with mono- nal IgM bands in the serum. Anti-idiotypic antisera ob- ned against the isolated IgM band proteins of both patients ved that the serum IgM band, the membrane IgM on the kemic lymphocytes, and the intracellular IgM in the plas- cells were idiotypically identical. The idiotypic determi- nts thus constitute tumor-specific antigens. Surface and racellular immunofluorescence studies using the idiotypic isera showed that certain cell lines from each patient were ived from the leukemic cells and others were derived from idual normal B lymphocytes. The leukemic lines contained ferent percentages of lymphoid cells with the idi- pe-specific membrane immunoglobulin (Ig) and different centages of plasma cells with intracellular Ig of the same cificity. Hemagglutination-inhibition analyses of cell line ernatants also demonstrated specific Ig synthesis. Aside m Ig specificity, there were no differences between the kemic lines and those derived from normal cells. After rox 6 mo of continuous culture, one leukemic cell line was ned in soft agarose. The cloning efficiency was approx %. Immunofluorescence studies of seven clones showed t all were of leukemic origin and that they had higher centages of cells positive for surface IgM than the parental e. (23 refs)

-7074 **A Case of AML Preceded by Fibrinous Bronchitis During the Preleukemic Phase.** (Jpn) Nunoue, N. (Second Dept. Internal Medicine, Showa Univ. Sch. Medicine, Japan); Kitamura, K.; Tomoyasu, S.; Asano, Y.; Yokoyama, S.; Tsuruoka, N.; Shimizu, M.; Sano, K. *Jpn J Clin Hematol* 19(9): 1226-1233; 1978.

A case of acute myelogenous leukemia (AML) preceded by the preleukemic phase, which developed following admission for fibrinous bronchitis, is reported. A 41-yr-old man presented with fever and recurrent attacks of dyspnea with expulsion of bronchial casts that lasted for several months and was diagnosed as fibrinous bronchitis. About a month after admission, a few abnormal leukocytes appeared in his blood smear. Bone marrow aspirates revealed: NCC 17.3 x $10^4/cm^3$, minimal bactericidal level 45.4%, and prothrombin 12.8%. A diagnosis of AML was confirmed. Review of the blood count from the onset of fibrinous bronchitis to the clinical manifestation of AML revealed progressive anemia with anisopoikilocytosis, and an episode of thrombocytosis, monocytosis, and reticulocytosis of unknown cause. The hematologic abnormalities that predated the development of AML were considered to be preleukemic in nature. (32 refs)

78-7075 **Quantitative Morphological Evaluation of Basal Lamina Changes During Epithelial Carcinogenesis (Meeting Abstract).** (Eng) White, F. H. (Dept. Oral Pathology, Univ. Sheffield, Sheffield, England); Gohari, K. *Clin Sci Mol Med* 55(3): 15P; 1978. (no refs)

78-7076 **Evidence for the Progressive Nature of Neoplastic Transformation In Vitro.** (Eng) Barrett, J. C. (Div. Biophysics, Sch. Hygiene and Public Health, Johns Hopkins Univ., Baltimore, MD, 21205); Ts'o, P. O. *Proc Natl Acad Sci USA* 75(8): 3761-3765; 1978.

Evidence is presented that neoplastic transformation in vitro is progressive, involving multiple developmental stages. Syrian hamster embryo cell cultures were treated with benzo(a)-pyrene (BP) and monitored for the acquisition of in vitro phenotypes associated with neoplasia. Morphological transformation and enhanced fibrinolytic activity were observed within 2 wk and anchorage-independent growth was observed after 6-15 wk. Development of the potential to grow in soft agar did not appear to be related to morphological transformation. One of four spontaneously established Syrian hamster embryo cell lines produced tumors in vivo. None of eight cultures treated with BP for 24 hr produced tumors, but all produced fibrosarcomas in 100% of injected animals after they had acquired anchorage independence in vitro. The data suggest that multiple cellular changes are required for the expression of anchorage-independent growth and that neoplastic transformation in vitro progresses through qualitatively different stages. The results strongly justify the study of oncogenesis in cell cultures as a model for neoplastic transformation in vivo. (24 refs.)

78-7077 **Genetics of the Large, External, Transformation-sensitive (LETS) Protein: Assignment of a Gene Coding for Expression of LETS to Human Chromosome 8.** (Eng) Owerbach, D. (Roswell Park Memorial Inst., New York State Dept. Health, Buffalo, NY, 14263); Doyle, D.; Shows, T. B. *Proc Natl Acad Sci USA* 75(11): 5640-5644; 1978.

The genetic basis of the large, external, transformation-sensitive (LETS) protein (fibronectin) was analyzed with the use of human-mouse somatic cell hybrids formed from human WI-38 fibroblasts and a mouse L-cell line not expressing LETS. External membrane proteins of these hybrids, which had reduced numbers of human but not mouse chromosomes, were labeled by lactoperoxidase-catalyzed iodination. Cell-surface proteins were identified after sodium dodecyl sulfate/polyacrylamide gel electrophoresis by autoradiography of the dried gel. The LETS protein was identified in parental human cells, and it segregated in the hybrids. The LETS protein segregated concordantly with the chromosome 8 enzyme marker glutathione reductase and human chromosome 8. In addition, dependence on cellular density and trypsin sensitivity were similar for LETS in the hybrid cells and in the human fibroblasts. These findings demonstrate that a gene, *LETS*, encoded on chromosome 8, is responsible for LETS protein expression in humans. Because LETS has been implicated in tumorigenicity and cellular transformation, it is of interest that rearrangement or modifications in the number of chromosome 8 have been associated with certain forms of cancer. (45 refs)

78-7078 **Hemodynamic Characteristics in Microcirculatory Blood Channels During Early Tumor Growth.** (Eng) Endrich, B. (Dept. AMES-Bioengineering, M-005, Univ. California at San Diego, La Jolla, CA, 92093); Intaglietta, M.; Reinhold, H. S.; Gross, J. F. *Cancer Res* 39(1): 17-23; 1979.

RBC velocity was determined in the microcirculation of the BA 1112 rat sarcoma and in regions located outside the tumor (repairing tissue), which were used as a control and were assumed to be representative of the inflammatory-reparative reaction of a healing wound. Studies were carried out in female Wistar rats of an inbred strain fitted with modified Algire window chambers utilizing television techniques in situ. Observations and measurements were started 14 days after implantation of tumor or adjacent tissue in the chamber and continued for 18 days. RBC velocity in repairing tissue was of the order of 0.80 ± 0.15 (S.E.) mm/sec in terminal arterioles, 0.2 ± 0.09 mm/sec in postcapillary venules, and 0.2 ± 0.1 mm/sec in collecting venules and remained constant during the observation period. By comparison, RBC velocity in terminal arterioles of the tumor tissue increased from 0.72 ± 0.08 to 0.95 ± 0.09 mm/sec and decreased slightly in postcapillary and collecting venules. Vasomotion in terminal arterioles of the malignant tissue could be demonstrated only until day 22 after implantation. Since vasomotion was observed only during the initial phase of tum growth and the arteriolar RBC velocity increased during t same period, the findings indicate that blood is supplied mesenchymal tumors by means of dilated arterioles. In adj cent repairing tissue (control), the RBC velocity of postcap lary and collecting venular remained constant. By compa son, RBC velocity decreased in venular outflow vessels of t tumor, suggesting that venous drainage is facilitated duri progressive spread of the BA 1112 sarcoma. (22 refs)

78-7079 **Cell Movement and the Mechanism of Invasiv ness: A Survey of the Behaviour of Some No mal and Malignant Cells Implanted into the Developi Chick Wing Bud.** (Eng) Tickle, C. (Dept. Biology as Applie to Medicine, Middlesex Hosp. Medical Sch., Cleveland S London W1P 6DB, England); Crawley, A.; Goodman, M *J Cell Sci* 31: 293-322; 1978.

Normal and malignant cells were implanted into the loo mesenchyme of developing chick wing buds to investigate th mechanisms of tumor invasiveness. Two to 3 days later, th distribution of the grafted cells was examined histologicall Cells from mouse lung tumor, rat bladder tumor, and huma breast tumor did not invade the mesenchyme, but trophobla tic, sarcoma 180, and neuroblastoma cells and cultured ham ster fibroblasts (BHK, PyBHK, Nil 8, HSV Nil 8) did. Cel from embryonic pigmented retina and heart ventricle we invasive. Thus, cell movement may not be a common featu of all invasive tumors. Lack of contact inhibition of mov ment, although probably involved in the invasiveness of sa coma 180 cells, did not appear to be necessary for invasio cells that exhibited contact inhibition of movement (BH and PyBHK) were also invasive. Both normal and tran formed cells (BHK and PyBHK; Nil 8 and HSV Nil 8) move into the mesenchyme. Other invading cells, such as troph blastic, neuroblastoma, and (to a small extent) HSV Nil cells, destroyed the adjacent host tissue, and this may be im portant in their invasiveness. Trophoblastic cells and the f broblasts were often elongated along the basement membran at the ectoderm/mesenchyme border and also closely ap posed to the endothelial linings of the blood vessels. Sarcom 180 and neuroblastoma cells clustered around nerves. Th embryonic tissues and neuroblastoma cells were often as sociated with blood vessels. A striking finding was that ca cinoma cells were frequently found positioned within th wing ectoderm on the basement membrane. This affinity o carcinoma cells for epithelium rather than the mesenchym suggests that the invasiveness of carcinomas involves th same mechanisms as the epithelial invasion of the mesen chyme that occurs during gland development. (77 refs.)

78-7080 **Banding Studies on Chromosomes in Diffus "Histiocytic" Lymphomas: Correlation 14q+ Marker Chromosome with Cytology.** (Eng) Fukuhar S. (Dept. Medicine, Univ. Chicago Hosp., 950 E. 59th St

ago, IL, 60637); Rowley, J. D.; Variakojis, D.; Sweet, . *Blood* 52(5): 989-1002; 1978.

omosomes were studied in involved lymph nodes of nine nts with diffuse histiocytic lymphoma. Two of the pa- s had stage II disease; their tumors were fibrotic and had itotic cells. One patient was in stage III, and the remain- ix patients had stage IV disease. The modal chromosome ber of abnormal cells from these last seven patients was diploid in two, hyperdiploid in four, and near-triploid ne. Complete banding studies, including peripheral blood bone marrow, of six cases, and partial analysis of the nth indicate that (1) every patient had a distinct cell line common markers, with a few cells showing minor vari- ; (2) although certain chromosomes (Nos. 1, 2, 3, 9, 12, 14) were structurally affected more often than others, no kers with the same banding pattern were noted among n; and (3) the cytologic type of lymphoma could be cor- ed with the karyotype in all seven patients. When the es and Collins classification was used, three patients se tumors were composed predominantly of large non- ved cells showed a 14q translocation leading to the forma- of a 14q+ marker chromosome. This marker was not rved in four patients whose tumors had a majority of e cleaved cells. These preliminary results suggest that e are consistent chromosome changes associated with ific subtypes of lymphoproliferative disorders analogous ne Philadelphia chromosome in chronic myelogenous leu- ia. (32 refs)

7081 **Effect of Microtubule Inhibitors on Malignant Invasion In Vitro.** (Eng) Mareel, M. M. (Dept. erimental Cancerology, Clinic Radiotherapy and Nu- r Medicine, Univ. Hosp., De Pintelaan 135, B-9000 nt, Belgium); De Brabander, M. J. *J Natl Cancer Inst*): 787-792; 1978.

malignant C3H/3T3 mouse cells MO_4 invaded embryon- nick heart fragments in an organotypic coculture system emisolid medium. Malignant invasion was obvious from rregular boundary between the MO_4 nodule and the heart ne, the penetration of strands and solitary MO_4 cells into heart, and destruction of the heart. In this system, at a e of 1 μg/ml, the microtubule inhibitors colchicine, deme- ine, vincristine sulfate, vinblastine sulfate, or me- [5-(2-thienylcarbonyl)-1H-benzimidazol-2-yl]carbamate codazole) totally inhibited malignant invasion. At this e the drugs were also mitostatic, which was apparent from itoses and from the absence of postmetaphase figures. At itostatic dose of 10 μg/ml, 5-fluorouracil (5-FU), cytosine inoside, or bleomycin did not interfere with malignant asion. Combined treatment of the cocultures with 5-FU μg/ml) plus Nocodazole (1 μg/ml) completely inhibited asion. These cocultures also showed the effective inhibi- of mitosis by 5-FU, because Nocodazole-induced C oses were absent. The reversibility of the anti- asive effect of a 4-day treatment with Nocodazole (1 μg/ml) was demonstrated in shaker cocultures with the use of fluid medium. These in vitro experiments indicate that cytoplasmic microtubules are involved in malignant invasion and that cell division and invasion constitute separate characteristics of malignant cells. (32 refs)

78-7082 **Evidence that the Malignant Lymphoma of Sjogren's Syndrome is a Monoclonal B-Cell Neoplasm.** (Eng) Zulman, J. (Immunology and Arthritis Section, Veterans Admin. Medical Center, 4150 Clement St., San Francisco, CA, 94121); Jaffe, R.; Talal, N. *N Engl J Med* 299(22): 1215-1220; 1978.

Nine patients who developed malignant lymphoma (ML) following Sjorgren's syndrome (SS) and antecedent benign salivary gland lesions were studied histopathologically and immunohistologically. Paraffin-embedded tissue blocks of malignant lymphoma were examined in all cases, and SS salivary gland lymphoid lesions in four. The unlabeled antibody-enzyme method (peroxidase antihorseradish peroxidase) was used for immunohistologic analyses. There were six female patients, the av age was 48 yr and the av duration from onset of SS to diagnosis of ML was 10 yr. Two patients received no irradiation or immunosuppressive therapy before ML development. Histologically, the tumors varied within themselves in cellular composition, content of epithelioid histiocytes, presence of plasmacytoid features, and numbers of plasma cells, but 6/9 patients had cytoplasmic immunoglobulin within the ML cells, confirming their B-cell nature. All six of these patients had IgMκ chains exclusively, but only one had rheumatoid arthritis, whereas all three patients who did not have IgMκ chains had rheumatoid arthritis. No tumor cells contained lysozyme, and none gave evidence of phagocytosis. These lymphomas could have arisen coincidentally with Sjorgren's syndrome or could represent a stage of B-cell dedifferentiation in which the concentration of intracytoplasmic immunoglobulin falls below a detectable threshold. (23 refs)

78-7083 **Familial Hodgkin's Disease.** (Eng) Hull, P. J. (Royal Infirmary, Manchester M13 9WL, England); Delamore, I. W. *Postgrad Med J* 54(636): 676-677; 1978.

The occurrence of Hodgkin's disease in a 23-yr-old man, his 22-yr-old sister, and their 13-yr-old cousin is reported. All had mediastinal involvement, and, in each case, the histology was that of nodular sclerosing Hodgkin's disease. (8 refs)

78-7084 **Membranous Proliferative Glomerulonephritis and Castleman's Lymphoma.** (Fre) Genin, R. (Clinique Medicale, Hopital du Bocage, F. 21034 Dijon

Cedex, France); Justrabo, E.; Devillebichot, C.; Michiels, R.; Rifle, G. *J Urol Nephrol (Paris)* 84(9): 667-672; 1978.

Castleman's pseudotumor, localized retroperitoneally and associated with membranoproliferative glomerulonephritis, was diagnosed in a 56-yr-old man. This association has never been reported before. A polyclonal plasmacyte population with IgA, IgG, and IgM was found in the tissue surrounding the lymph nodes involved. Disappearance of proteinuria and regression of the nephrotic syndrome were seen after the pseudotumor was removed. Castleman's pseudotumor is very rare; only 200 cases have been reported hitherto. It affects men and women alike, mostly during the second and third decades of life. While a fortuitous association of the two diseases cannot be ruled out, the glomerular affection may be due to the presence of angiofollicular hyperplasia, as are the frequent immunological and hematological manifestations. Thus, the nephropathy may be due to the production of circulating immunocomplexes. According to another hypothesis, the two diseases may have a common etiological factor. Castleman's pseudotumor was found in some cases following vaccination or the resorption of suture material. Bacterial or viral etiology has not been proved. The patient presented here had a facial wound about 2 mo before the onset of glomerulonephritis, which may have been the port of entry of an antigen. (9 refs)

78-7085 **Development of the Granulomatous Response in Murine Toxocariasis.** (Eng) Kayes, S. G. (Veterans Admin. Hosp., 1310 24th Ave., South, Nashville, TN, 37203); Oaks, J. A. *Am J Pathol* 93(2): 277-294; 1978.

To characterize the cellular evolution of muscle-associated granuloma in murine toxocariasis, *Toxocara canis* eggs were collected from the stools of naturally infected puppies, cultured, checked for the presence of stage 2 (L2) infective larvae, and administered to male HM/ICR mice (1,000 eggs/mouse) by stomach intubation. Necropsies were performed between 11-14, 28-35, and 70-77 days postinfection, and the carcas musculature was examined by light and electron microscopy following appropriate histologic preparation. By day 11, the initial granulomas consisted primarily of eosinophils. By day 14, many of the eosinophils appeared to be dying and undergoing disintegration; the resulting cellular debris was sometimes seen inside macrophages. Two distinct lesions were observed during the 28-35 day interval: the first, representing a continuation of the evolving mononuclear progression seen at day 14 and containing predominantly macrophages, was outlined by fibroblasts and enveloped in a distinct collagenous capsule; the second lesion day contained foci of polymorphs and mononuclear cells similar to those seen at 11-14 days. By 77 days, the granulomas had developed into fibrotically encapsulated epitheloid lesions surrounding the larva. The results indicate that infection by this parasitic larvae nematode progresses from an inflammatory reaction to a loose eosinophil-containing exudate, and, finally, to a compacted, encapsulated granuloma, a situation likened hepatic granuloma and schistosome egg granuloma. (36 re

78-7086 **Studies on a Japanese Burkitt Lymphoma. Pa 2: Serial Transplantation of a Japanese Burki Lymphoma Cell Line in Hamsters.** (Jpn) Kishimoto, (Dept. Internal Medicine, Okayama Univ. Medical Sc Okayama, Japan). *Jpn J Clin Hematol* 19(9): 1186-119 1978.

An Epstein-Barr virus genome-free Japanese Burkitt lyr phoma line (JBL) was transplanted ip for 10 serial passag in newborn Syrian hamsters treated with antilymphocy serum. All the hamsters developed invasive tumors and ma sive ascites. The hamster-passaged line maintained a chara teristic starry-sky pattern closely resembling that of huma biopsy material. Some of the animals developed not only bo marrow invasion but also a leukemic blood picture. Since t JBL line was converted to an ascitic form, its serial passa was greatly facilitated. (13 refs)

78-7087 **Possible Role of Connective Tissue in Epide mal Neoplasia.** (Eng) Mitrani, E. (Dept. Med cine, Welsh Natl. Sch. Medicine, Heath Park, Cardi Wales). *Br J Dermatol* 99(3): 233-244; 1978.

Interactions between epidermal cells were defined within proposed mathematical model of mammalian skin. Examin tion was made of how epidermis retains its mass both norma ly and after various disturbances and how this mechanis may fail, as in neoplasia. The model assumes that the low the epidermal layer (ie, nearer the dermis), the higher t probability of a cell in that layer to enter mitosis. Compute tests of the model suggested that in highly proliferating ep dermis, competition for cell space in the basal layer may b sufficient to generate considerable forces in the papillary de mis. According to data on human and pig epidermal hype plasia, basal cells are submitted to considerable lateral force and these and not dermal hyperplasia or dermal edema a the forces responsible for the increasingly folded dermoep dermal junction. In the condition of a persistently high mito ic rate, the model remains stable only if new connective tissu (collagen) synthesis is not induced by the developing papi lary tension. New collagen tissue formation relieves the stre only temporarily; then the epidermis is in a situation simil to the one prevailing before synthesis began, except that has induced a given amount of dermal growth. Thus, self-expanding system emerges. Clearly, collagen synthes plays an important role in epithelial neoplasia. (38 refs)

78-7088 **A Causal Relation Between Bowen's Diseas and a Lewisite Scar.** (Ger) Krause, H. (A teilung Dermatologie der Medizinischen Fakultat, Technisc

Hochschule, Goethestrasse 27-29, D-5100 Aachen, W. many); Grussendorf, E. I. *Hautarzt* 29(9): 490-493; 1978.

an developed Bowen's disease of the right lower leg 8 fter accidental contact of that area with Lewisite (mus- gas). The tumor excision was followed by a local recur- e 2 yr later. (25 refs)

089 **Basal Cell Epithelioma in a Vaccination Scar.** (Eng) Hazelrigg, D. E. (Section Dermatology, born Clinic, 421 Chestnut St., Evansville, IN, 47713). *Dermatol* 17(9): 723-725; 1978.

-yr-old woman developed a superficial basal cell epitheli- (BCE) in a smallpox vaccination scar. She had been inated at 12 yr of age. Two BCE's had been removed the posterior neck and forehead 2 and 1 yr before the nt presented with the lesion described. The latter had rged gradually over 6 yr. (12 refs)

090 **DNA Repair Deficiency in Lymphocytes from Patients with Actinic Keratosis.** (Eng) -Darub, J. M. (Dept. Biochemistry and Dermatology, . Glasgow, Glasgow, G12 8QQ, Scotland); Mackie, R.; , J. D. *Bull Cancer (Paris)* 65(3): 357-362; 1978.

A repair activity in peripheral blood lymphocytes was sured in 18 patients with actinic keratosis (AK) and 18 matched controls by comparing the incorporation of hymidine into UV-irradiated cells with that into nonir- ated cells. The incorporation was followed by autoradiog- y or scintillation spectrometry. The rate of incorporation H-thymidine (5.0 μCi/ml, 18.5 Ci/mmole) into hydrox- a treated (1.5 x 10^{-3}m) AK lymphocytes measured at rent times after irradiation of 20 Joules (J)/meter^2(m^2) 54 nanometers was constantly lower than that into nor- cells at all times examined. When UV dose response was ied by measuring total incorporation of ^{3}H-thymidine lymphocytes at different UV doses 4 hr after irradiation, ir activity of AK cells was approx 50% that of controls l UV doses examined. For both cell populations, the re- curve plateaued between 10 and 20 J/m^2. Autoradio- hic analysis of AK lymphocytes after irradiation at 5.0 20 J/m^2 determined the av UV-induced DNA repair syn- s to be 47.7% and 48.9% of normal lymphocytes, respec- y. Measurement of the differential of total incorporation H-thymidine into hydroxyurea-treated and untreated pa- and control lymphocytes after 20 J/m^2 irradiation reaf- ed a DNA repair rate of 41%-56% that of normal con- . The results of using two different analytical methods xamine DNA repair are quite similar and show that the of repair in AK cells are all in the range 38-63% that ormal cells. (12 refs)

78-7091 **DNA Repair in Conditions Associated with Malignancy: Aging and Actinic Keratosis.** (Eng) Ringborg, U. (Radiumhemmet, Karolinska Hosp., S-104 01 Stockholm 60, Sweden); Lambert, B.; Swanbeck, G. *In: Third International Symposium on the Detection and Prevention of Cancer held by the International Study Group for the Prevention and Detection of Cancer in New York, April 26-May 1, 1976.* International Study Group for the Prevention and Detection of Cancer (New York, NY): Vol. 1(part 1): pp. 1193; 39-52; 1977.

UV light-induced DNA excision repair was studied in two conditions associated with malignancy, aging and actinic keratosis, in an attempt to clarify the relationship between a decreased capacity for DNA repair and malignant disease. WBC from 48 healthy subjects aged 13-94 yr were irradiated with 3.2, 6.4, 9.6, or 19.2 joules/m^2 UV light and incubated with ^{3}H-thymidine in the presence of hydroxyurea. There were great variations in max incorporation of ^{3}H-thymidine among individuals, and they were considered biological in origin. For the three higher UV doses, DNA repair synthesis was signficantly lower in subjects 60-94 yr old than in subjects 13-59 yr old. The av DNA repair capacity decreased by about 30% between 20 and 90 yr of age. WBC from 10 patients with actinic keratoses (5 men, 5 women aged 53-81) and from 10 healthy controls of the same age range were subjected to the same treatment as above. The capacity for DNA repair synthesis was 30% lower in the actinic keratosis patients than in the controls. The possibility that the reduced capacity for DNA repair in aging and actinic keratosis predisposes an individual to malignant disease is discussed. (14 refs)

78-7092 **Posttraumatic Epithelioma.** (Ita) Fallica, L. (Clinica Dermosifilopatica, Universita di Catania, Catania, Italy); Guarneri, B. *G Ital Dermatol* 113(7/8): 477-479; 1978.

Three patients (two men, one woman, aged 70, 62, and 56 yr, respectively) developed basal-cell carcinoma of the skin after mechanical trauma of the same site. The latency from the trauma to the manifestation of the carcinoma was 7-15 mo. Literature data, as well as the rarity of posttraumatic carcinomas, suggest that the trauma only accelerates the development of the neoplasia as a function of a quantitative modification of the cells that are qualitatively already anaplastic, ie, that trauma acts only as a promoting factor. (13 refs)

78-7093 **Hydatidiform Mole as a Complication of Artificial Insemination.** (Eng) Stone, S. C. (Dept. Obstetrics and Gynecology, Univ. California at Irvine, 101 City Drive S., Orange, CA, 92668). *Am J Obstet Gynecol* 132(6): 696-697; 1978.

A hydatidiform mole developed in a 22-yr-old woman who

had undergone artifical insemination with fresh donor sperm. A spontaneous abortion occurred at 8 wk gestation, and scanty tissue of molar appearance was passed. The pathology report confirmed the diagnosis of molar pregnancy. (2 refs)

78-7094 **Naevoid Basal Cell Carcinoma Syndrome and Charcot-Marie-Tooth Disease: Two Autosomal Dominant Disorders Segregating in a Family.** (Eng) Heimler, A. (Div. Human Genetics, Dept. Pediatrics, Long Island Jewish-Hillside Medical Center, New Hyde Park, NY, 11040); Friedman, E.; Rosenthal, A. D. *J Med Genet* 15(4): 288-291; 1978.

A family is described in which 16 members (three generations) have Charcot-Marie-Tooth disease; at least six members also have nevoid basal cell carcinoma syndrome (NBCS), and one member with both disorders has two daughters with NBCS. These two disorders have not been reported previously in the same patient or within one family. A diagnosis of NBCS should be considered in any patient with recurrent dentigerous cysts at an early age. (8 refs)

78-7095 **Pathogenesis of Prolactin-secreting Pituitary Adenomas.** (Eng) Sherman, B. M. (Clinical Res. Center, Univ. Hosps., Iowa City, IA, 52242); Schlechte, J.; Halmi, N. S.; Chapler, F. K.; Harris, C. E.; Duello, T. M.; VanGilder, J.; Granner, D. K. *Lancet* 2(8098): 1019-1021; 1978.

In a comprehensive multidisciplinary study of pituitary tumors, 42 women (aged 18-54) with amenorrhea and hyperprolactinemia [25-833 nanograms (ng)/ml] related to a pituitary adenoma were studied. Seventy-four percent of these patients developed amenorrhea and/or galactorrhea in immediate association with the use or discontinuation of oral contraceptives (24 women) or postpartum (7 women). All underwent transsphenoidal surgery for resection of the tumor, and there was enough adenomatous tissue for immunocytochemical studies in 35 specimens. Prolactin was localized unequivocally in 31 specimens by immunoperoxidase staining with anti-rat prolactin serum. The mean serum prolactin concentration did not differ in the groups with and without galactorrhea, but it was significantly greater in the 15 patients with adenomas 10 mm or more in diameter (226 ng/ml) than in those with lesions < 10 mm (94 ng/ml). The authors suggest that estrogens, which modulate prolactin secretion in normal humans and animals, can induce the growth and expression of otherwise silent pituitary lesions and that this should be considered a risk of oral contraceptive use. (17 refs)

78-7096 **Meningiomas in Five Members of a Family over Two Generations, in One Member Simultaneously with Acoustic Neurinomas.** (Eng) Delleman, J. V (Ophthalmogenetic Dept., Netherlands Ophthalmic Re Inst., Wilhelmina Gasthuis, Amsterdam, Netherlands); I Jong, J. G.; Bleeker, G. M. *Neurology (Minneap)* 28(6 567-570; 1978.

The familial occurrence of meningioma in five members a family over a two-generation span is reported. The proba was a 33-yr-old man who had undergone enucleation of t left eye at age 22 yr; a meningioma psammomatosum of t optic nerve sheath, with infiltration of the surrounding tissu was found. Two recurrences were noted over the next 5 y A sister had a spinal meningioma removed at age 25 and hyperostotic meningioma removed at age 31. The proban father and uncle also had meningiomas. None of these fo had evidence of neurofibromatosis. The autopsy report o paternal aunt who had died at the age of 43 indicated th she had bilateral acoustic neurinomas and multiple menin omas. A sister of the proband has multiple cafe-au-lait spo It is suggested that all these cases are manifestations neurofibromatosis. (55 refs)

78-7097 **Possible Maternal Effect on Severity Neurofibromatosis.** (Eng) Miller, M. (De Medicine and Pediatrics, Univ. Washington Sch. Medicin Seattle, WA, 98105); Hall, J. G. *Lancet* 2(8099): 1071-107 1978.

A review of medical records of patients under 18 yr old se for signs or symptoms suggestive of neurofibromatosis vealed 62 patients (from 54 families) with the disease w were then assessed for severity of disease and whether t individual was the result of a new mutation or born to affected father or mother. Patients were considered to ha this autosomal dominant disease if they demonstrated cafe-au-lait spots > 1.5 cm in diameter. Severity of disea was graded on a 0-3 scale based on physical and men parameters. The expected numbers of new mutations and p tients born to affected mothers or fathers (based on gene probabilities and relative fertilities) was compared with t observed cases; 16 patients had new mutations, compar with an expected number of 31, 15 were born to an affect father compared with an expected 11, and 31 were born an affected mother, compared with an expected 20. The me severity of disease was highest in those born to affected mo ers (2.4), least in those born to affected fathers (0.8), a intermediate in new mutations (1.6). Cases due to new mu tions or born to affected fathers were relatively evenly d tributed among the four grades of severity, but significan more of those born to affected mothers had severe compli tions. The 21 cases with severe complications born of affect mothers tended to present the disease early in childhood. F thermore, in the six instances in which two affected sibs w born to an affected mother, all suffered the most severe fo of complications. It is suggested that the severity observ in cases born to affected mothers is due to some factor in t intrauterine environment produced by the affected moth

interacts only with fetuses that carry the neurofi-natosis gene. This interaction may be humorally mediat- (10 refs)

7098 **Ulcer of the Tongue after CCNU Therapy for a Spinal-Cord Tumor.** (Eng) Walker, M. D. ain Tumor Study Group, NCI, Bethesda, MD, 20014); hardson, E. P.; Scully, R. E. *N Engl J Med* 299(19): 0-1067; 1978.

7-yr-old woman with a history of hepatitis and pelvic ture 1 yr before admission presented with pain in the arm. was diagnosed with an intradural-extramedullary, mixed ocytoma/ependymoma-type glioma of the spinal cord. r the next 3 yr, she received 12 doses of 1-(2-chloroe-)-3-cyclohexyl-1-nitrosourea because of the growth of ignant glial cells in cerebrospinal fluid cultures. Upon sec- admission, she developed general debility secondary to amous cell carcinoma, with metastases to cervical lymph es, lungs, and pleuras. Anatomical diagnosis also revealed yelinative quiescent myelopathy and cavernous hemangi- s of the liver. (5 refs)

7099 **Enzymes of Neutrophils from Patients with Precancerous States of the Larynx.** (Eng) Lisiew- J. (Dept. Hematology, Inst. Internal Medicine, Cracow d. Medicine, Cracow, Poland); Gierek, T.; Pilch, J.; Pias- ka, B.; Namyslowski, G. *Rev Esp Oncol* 25(1): 7-11; 1978.

levels of β-glucuronidase, alkaline and acid phospha- s, N-acetyl-β-glucosaminidase (NAGA), myeloperoxi- e, glycogen, and lipids in the peripheral blood neutrophils 0 healthy men and 24 men with precancerous states of larynx (leukoplakia, papillomas, or pachydermia) were pared. The patients and healthy controls did not differ erms of absolute total neutrophil counts or absolute nts of neutrophils staining for β-glucuronidase, acid phos- tase, NAGA, myeloperoxidase, PAS, or lipids. However, n values of neutrophilic leukocytosis, the absolute count alkaline phosphatase-positive neutrophils, and alkaline sphatase activity were significantly higher in the patients n in the controls. In contrast, intracellular β-glucuroni- e activity and lipid content were significantly lower in the ients. (11 refs)

7100 **Mucoepidermoid Tumor of the Epipharynx.** (Ger) Nowak, R. (Klinik und Poliklinik fur s-, Nasen- und Ohrenkrankheiten, Wilhelm-Pieck-Uni- sitat, Doberanerstrasse 139, DDR-25 Rostock 1, E. Ger- ny); Putzke, H. P. *Arch Otorhinolaryngol (NY)* 221(3): -233; 1978.

nucoepidermoid tumor of the epipharynx was diagnosed biopsy in a 39-yr-old woman. She developed a local recurrence about 1 yr after tumor resection. Histopathological investigation revealed that the primary tumor consisted mainly of undifferentiated cells, plus glandular duct and acinar epithelial cells and epidermoid cells at various stages of maturity. The findings suggest that these tumors originate from pluripotent cells of the transition between the acinus and duct, rather than from major glandular and salivary ducts. They are classified as being of low-grade malignancy. (12 refs)

78-7101 **Intracisternal Tubular Inclusions in Nasopharyngeal Carcinoma.** (Eng) Prasad, U. (E.N.T. Dept., Faculty Medicine, Univ. Malaya, Kuala Lumpur, Malaysia); Gogusev, J. *J Laryngol Otol* 92(11): 979-989; 1978.

Twenty biopsy specimens from patients with nasopharyngeal carcinoma were examined ultrastructurally for the presence of intracisternal tubular inclusions (ITI). These inclusions were observed in the cytoplasm in eight cases. The tubules were arranged in reticular arrays. Dense particles with an outer diameter of 200 A were interconnected by light bands, and these aggregates were bound by a membrane that was continuous with the granular endoplasmic reticulum (GER). In five other cases, a slightly different type of cytoplasmic inclusion was found. The inclusion was large and almost spherical, with filamentous aggregates criss-crossing in a haphazard way. The aggregates seemed to be connected to the GER. ITI may be the result of an immunological reaction initiated by injured cells infected with Epstein-Barr virus, which acts as an antigen. (37 refs)

78-7102 **Radiation-induced Carcinoma of the Thyroid with Severe Thyrotoxicosis.** (Eng) Citrin, D. L. (Dept. Human Oncology, 701C Univ. Hosps., 1300 Univ. Ave., Madison, WI, 53706); Pederson, J.; Rose, D. P.; Carbone, P. P. *Wisconsin Medical J* 77(10): 597-599; 1978.

The case of a 65-yr-old woman with radiation-induced metastatic thyroid cancer and severe thyrotoxicosis is presented. The patient had received radiation therapy to the neck and upper chest at age 8 yr. During the year prior to presentation, there was a rapid increase in the size of a neck mass that had been present for many years. The patient had taken thyroxine intermittently during these years but had taken no thyroid medication for at least 3 yr prior to presentation. The patient presented with complete dysphagia. Hyperkinesis, tremor, and atrial fibrillation suggested hyperthroidism; this was supported by thyroid function tests, but the patient was unable to swallow the ^{131}I for a radioiodine uptake test. Biopsy of the neck mass revealed a mixed follicular and papillary thyroid carcinoma. The firm, nontender mass measured at least 10 x 10 cm and formed a firm collar around the trachea, which could not be clearly identified. Postmortem examination showed that the left lobe of the thyroid gland measured

10 x 5 cm and contained necrotic areas. The right lobe was also involved, with invasion of the capsule and neck muscles. Histologic examination revealed a well-differentiated follicular and papillary carcinoma with colloid present in the follicles. There was no evidence of hyperplastic normal thyroid tissue. The lungs were filled with metastatic thyroid nodules up to 2 cm in diameter. In previously irradiated patients, hyperthyroidism does not exclude the possibility of thyroid cancer. (6 refs)

78-7103 **Morphological Aspects of Parathyroid Transplantation. Clinical Relevancy of Induced Invasive Tissue Growth.** (Ger) Klempa, I. (Abteilung fur Allgemein- und Abdominalchirurgie, Zentrum der Chirurgie der Universitat, Theodar-Stern-Kai 7, D-6000 Frankfurt/Main, W. Germany); Steinau, U.; Frei, U.; Koch, K. M.; Usadel, K. H.; Rottger, P. *Chirurg* 49(11): 704-710; 1978.

A 40-yr-old man with hypercalcemia and increased parathyroid hormone levels due to terminal renal insufficiency underwent total parathyroidectomy following which one of the parathyroid glands (showing typical adenomatous hyperplasia without signs of potential or manifest malignancy) was grafted in the forearm. The autograft started growing rapidly 5 mo after grafting, and the serum calcium and parathyroid hormone levels increased. An autonomous tumor-like adenomatous formation measuring 2.5-3 cm in diameter and weighing 3.1 g was excised 9 mo after the implantation. The parathyroid tissue excised showed solid, relatively cell-rich growth interspersed with giant nuclei. The tumor invaded the vessels of the normal muscular tissue. The findings suggest that induced invasive tissue growth is possible following parathyroid autografting and that only parathyroid tissue without adenomatous hyperplasia should be used for this purpose. (16 refs)

78-7104 **Growth of Murine Mammary Tumor Cells in an Artificial Capillary System: Ultrastructural Study.** (Fre) Mouriquand, J. (Laboratoire d'Histologie, Cytologie et Cytogenetique, Faculte de Medecine de Grenoble, 38700 La Tronche, France); Mouriquand, C.; Mermet, M. A.; Louis, J.; Petitpas, E. *Biol Cell (Paris)* 31(1): 27-30; 1978.

A method is described for growing murine mammary tumor cells on an artifical capillary system. The cells were from spontaneous mammary tumors in the PS strain of mice. Actually, the cells had reverted to epithelial morphology since they were in the 162nd passage. The artificial capillary system used copolymers of acrylic or polysulfone permeable to substances of mol wt up to 50,000 or 100,000, respectively. The cells were grown in a medium containing 10% decomplemented calf serum, penicillin and streptomycin. Light and electron microscopy was used to monitor growth of the cells in the wk 3-5. Epithelial clumps could be seen between the capillaries or clustering against them. Murine mammary t
mor virus (MTV) particles were numerous, with A-type pa
ticles in the cytoplasm and B-type particle in the vacuol
in the intercellular spaces and free in the culture mediu
Intracytoplasmic ductlike vacuoles similar to those describ
in human breast cancer cells were observed, and it is believ
that these have not previously been reported in murine ma
mary tumor cells. (43 refs)

78-7105 **Cytology of Secretions and Aspiration Biopsie
Diagnostic Applications in Mammary Disease**
(Ita) Magni, E. (Servizio di anatomia e istologia patologic
Ospedale Civile S. Maria delle Croci, Ravenna, Italy); Mon
G.; Tabarri, B. *Pathologica* 70(1007/1008): 495-502; 1978

Secretion cytology was performed in 1,780 women wi
mammary secretion, and needle biopsy was performed in 7
women with palpable breast nodes. The secretion cytolo
was indicative of pathological changes: the cytologic
changes were rated as grade III in 24 cases; papilloma w
diagnosed histologically in 19/24 cases, papillomatosis in
and intraductal carcinoma in 1. The cytological findings we
rated as grade IV-V in 15 cases: intraductal carcinoma w
found histologically in 6 cases and invasive carcinoma in
The needle biopsy, performed in 395 women with solid nod
and in 357 patients with cystic nodes, failed to reveal tum
cells in any of the cysts. The reliability of needle biopsy w
studied in 184 histologically verified cases: the histology r
vealed malignant tumors in 75 cases; the cytological findin
were concordant with the histology in 62 cases, false negati
in 5, and 8 biopsies were unevaluable. In 109 histological
negative cases, the biopsy was correctly negative in 85 case
false positive in 4, and 20 biopsy specimens were unevaluabl
The findings indicate the great diagnostic value of secretio
and biopsy cytology in the diagnosis of breast diseases.
refs)

78-7106 **Prevalence of Hypertension and Diabetes
Breast Cancer: A Case-Control Study in 179 P
tients and Age-matched, Non-hospitalized Controls.** (En
Adami, H. O. (Dept. Surgery, Univ. Hosp., S-750 14 Up
sala, Sweden); Rimsten, A. *Clin Oncol* 4(3): 243-249; 197

The prevalence of hypertension and diabetes was investigate
in 179 consecutive breast cancer patients (mean age, 63 y
seen in four Swedish counties during a 5-mo period and 17
age-matched controls. Pertinent information was gathered b
questionnaire, hospital records, and by interview. The bloo
pressure of all subjects was measured, and blood sampl
were taken for hormone analyses. Thirty-three patients an
28 controls were premenopausal. Hypertension was found i
33.5% of the patients and 32.4% of the controls. The distr
bution of systolic and diastolic blood pressure in the patien
was in close accordance with that in the controls, even whe
the women were subdivided into pre- and postmenopaus

tegories. Age was significantly correlated with diastolic and stolic blood pressure. The use of antihypertensive drugs as similar in the two groups. The prevalence of diabetes was so similar: 10 patients (9 under treatment) and 8 controls ll under treatment). Apparently, there is no association be-veen breast cancer and hypertension or diabetes. (27 refs)

8-7107 **Fibrocystic Breast Disease in Oral-Contraceptive Users. A Histopathological Evaluation of ithelial Atypia.** (Eng) LiVolsi, V. A. (Dept. Pathology, le Univ. Sch. Medicine, New Haven, CT, 06510); Stadel, V.; Kelsey, J. L.; Holford, T. R.; White, C. *N Engl J Med* 9(8): 381-385; 1978.

case-control study was performed to determine whether e association between oral contraceptive (OC) use and fi-ocystic disease (FD) varies according to the extent of epi-elial atypia associated with the latter. The patients, 205 emenopausal women aged 20-44 yr, and individually atched controls had been admitted as in- or outpatients to o Connecticut hospitals during 1971-1973. The frequency FD was not differentially associated with prior OC use hen cases were subdivided according to histologic patterns one. However, there were variations in the frequency of FD nong long-term pill users compared with nonusers accord-g to the degree of epithelial cytologic atypia being consid-ed. The results support the hypothesis that the use of OC r 2-4 yr or more is associated with a decreased frequency FD with only minimal epithelial atypia, and not with the ore florid forms of this condition. These findings suggest at a spectrum of cystic disease exists and that the long-term e of OC protects against the forms of FD that are not firmly sociated with an increased risk of breast cancer, but not gainst the premalignant forms. (40 refs.)

8-7108 **Volume and Hyperplastic Lesions of Breast of Japanese Women in Hawaii and Japan.** (Eng) asano, N. (Dept. Pathology, Tohoku Univ. Sch. Medicine, ndai, Japan); Tateno, H.; Stemmermann, G. N. *Prev Med* (2): 196-204; 1978.

reast volume and the frequency of ductal hyperplasia were etermined in autopsy subjects in Japan and Hawaii. The olume of the total breast (TBV) and of the mammary gland as calculated from specimen radiographs of serially sliced reasts enucleated at necropsy. TBV had a relatively good rrelation with the Quetelet index (body wt/height squared) cept among Japanese women <45 yr of age. Glandular olume had no significant correlation with the Quetelet index cept in Japanese women ≥ 45 yr. In Hawaiian women, the BV decreased until 39 yr of age and thereafter showed little ange. In Japan, the TBV showed a conspicuous decrease old age, possibly due to a loss of adipose tissue. In remenopausal women, mean values of glandular breast volume decreased up to 49 yr of age in parallel with the TBV. The volume density increased slightly from puberty to 39 yr; it then decreased and stabilized at a lower level after 40. Women with premenopausal oophorectomy had volume density values within the standard deviation, but they had a smaller mean value. Women with postmenopausal oophorectomy had generally low values. Epithelial hyperplasia was much more common in Hawaiian than Japanese women after age 30. The Hawaiian women were divided into native-born issei and Hawaiian-born nisei. A total of 19/37 nisei showed epithelial hyperplasia; this incidence (51.4%)was far higher than that in the issei (14.5%) and in Japanese women (18.7%). In Hawaiian women aged ≥ 45 yr, the volume of the mammary gland, corrected by the Quetelet index, was larger when epithelial hyperplasia was present than when it was absent. Women with premenopausal oophorectomy had no epithelial hyperplasia. (4 refs)

78-7109 **Metastases In Vitro: Assays for Cell-release and Invasion (Meeting Abstract).** (Eng) Li, A. P. (Cancer Res. and Treatment Center, Univ. New Mexico, Albuquerque, NM, 87131). *Proc Am Assoc Cancer Res* 19: 55; 1978. (no refs)

78-7110 **Transformed Cell Lines Susceptible or Resistant to In Vivo Surveillance Against Tumorigenesis.** (Eng) Patek, P. Q. (Developmental Biology Lab., Salk Inst., P.O. Box 1809, San Diego, CA, 92112); Collins, J. L.; Cohn, M. *Nature* 276(5687): 510-511; 1978.

Steps involved in the transformation of a normal cell to a malignant one were investigated by transforming normal continuous cell lines in vitro and selecting for transformants by their growth in agarose. The tumorigenicity of the cloned, transformed cell lines was tested in normal and immunodeficient (ID) mice. Based on tumorigenic potential, the cells were divided into three classes: O, growth in agarose only; I, growth in agarose + tumor formation in ID mice; C, growth in agarose + tumor formation in normal and ID mice. Normal fibroblast cells (N) derived from BALB/c, BALB.B, and C57BL/6 embryo cultures were transformed virally (simian virus 40 or Abelson murine leukemia virus) or chemically (20-methylcholanthrene, N-methyl-N′-nitro-N-nitrosoguanidine, 11,12-dihydro-3-methylcholanthrene-11,12-epoxide or 5,6- dihydrobenz(a)anthracene-5,6-epoxide). Of 14 agarose-positive cell clones derived from viral transformation, 2 were classified O, 9 I, and 3 C. Of 21 clones derived from chemical transformation, 2 were classified O, 4 I, and 15 C. Overall, 31/35 agarose-positive clones formed tumors in ID mice; ie, there was an 89% correlation between in vitro growth in agarose and in vivo tumorigenicity. The proportion of I tumorigenic transformed lines was 9/12 for the virally transformed lines and 4/19 for the chemically transformed lines. Expressed in terms of surveillance efficiency, 75% of

the former and 21% of the latter were susceptible to a surveillance mechanism that was impaired in ID mice. It is not known whether all C lines are derived from I intermediates; however, clones that have undergone the mutation N to I require another mutation, I to C, to grow as a tumor in normal mice. (7 refs)

78-7111 **Lymphoma after S.L.E. (Letter to Editor).** (Eng) Gibbs, A. R. (Dept. Pathology, Welsh Natl. Sch. Medicine, Cardiff CF4 4XN, Wales); Seal, R. M. *Lancet* 2(8098): 1046; 1978.

Primary pulmonary malignant lymphoma developed in a 57-yr-old woman 20 yr after the onset of systemic lupus erythematosus, the first published case of this association. Microscopy revealed a nodular, poorly differentiated-type non-Hodgkin's lymphoma. (no refs)

78-7112 **Needle Tract Implantation in a Case of Needle Biopsy for Lung Cancer.** (Eng) Ichiba, M. (Dept. Surgery, Tokyo Medical Coll., 6-7-1, Nishishinjuku, Shinjuku-ku, Tokyo 160, Japan); Aida, M.; Konaka, C.; Hayata, Y. *Jpn J Clin Oncol* 8(1): 71-73; 1978.

A pulmonary adenocarcinoma was implanted in the tract of a small-bore needle biopsy in a 60-yr-old man. It was diagnosed 19 mo after the original biopsy. This was the first case of tumor cell implantation encountered among a series of 582 biopsies and it is the eighth case reported in the literature. (13 refs.)

78-7113 **Etiology of Malignant Pericardial Mesothelioma.** (Ger) Eck, H. (Pathologisches Institut, Stadtisches Krankenhaus Hochst, Gotenstr. 6-8, 6230 Frankfurt 80, W. Germany); Berg-Schlosser, V. *Dtsch Med Wochenschr* 103(44): 1751-1753; 1978.

Malignant mesothelioma of the pericardium was diagnosed in a 45-yr-old man and in a 77-yr-old woman. Mild lung fibrosis and a slightly but significantly increased number of asbestos needles in the pulmonary parenchyma were found in the 45-yr-old man who, being a scrap dealer, may have been exposed to asbestos occupationally; however, other unknown etiological factors must also have been involved. No asbestos bodies were found in the 77-yr-old woman, but hemosiderin, obviously originating from phagocytized erythrocytes, was found in the tumor cells. This phagocytic activity of the mesothelial cells seems to be a proof of the mesothelial origin of such tumors. (9 refs)

78-7114 **Epithelial Dysplasia in Cancerous and Noncancerous Esophagi.** (Eng) Sato, E. (Second Dept. Pathology, Kagoshima Univ. Faculty Medicine, Kagoshima 890, Japan); Tokunaga, M.; Sakae, K.; Mukada, T.; Sasano, N. *Tohoku J Exp Med* 124(2): 117-128; 1978.

The prevalence, severity, distribution, and histology of esophageal dysplasia were studied in 86 grossly normal human specimens obtained at necropsy and in 100 specimens of esophageal carcinoma obtained at surgery. Fifty-four of the necropsy specimens showed dysplasia, 32 from men and 22 from women. Seventeen men and three women showed moderate or severe dysplasia or carcinoma in situ (CIS). The incidence and severity of dysplasia seemed to increase with alcohol and cigarette use, but the results were inconclusive. The incidence and severity also increased with age. Chronic inflammation, glycogenic acanthosis, and hyperplasia of the duct epithelium were observed frequently, but they were not significantly related to the incidence of dysplasia. Most of the surgical specimens showed a more advanced dysplasia. Those that showed extensive dysplasia tended to have a mosaic pattern of CIS and dysplasia. Carcinoma and extensive dysplasia was found in 24 instances, carcinoma and multifocal dysplasia in 46. Of the 24 cases that did not have treatment prior to surgery, 15 showed dysplasia coexisting with the carcinoma, and 19 showed multicentric foci of carcinoma. The invasive carcinoma sometimes did not show a sharp demarcation from the surrounding mucosa, especially in cases involving well-differentiated squamous cell carcinoma. The results indicate that dysplasia plays a significant role as a precursor lesion in esophageal carcinogenesis. (19 refs)

78-7115 **Conversion of a Poorly Differentiated Human Adenocarcinoma to Ascites Form with Invasion and Metastasis in Nude Mice: Brief Communication.** (Eng) Takahashi, S. (First Dept. Surgery, Nara Medical Univ., 840 Shijo-cho, Kashihara, Nara 634, Japan); Konishi, Y.; Nakatani, K.; Inui, S.; Kojima, K.; Shiratori, T. *J Natl Cancer Inst* 60(4): 925-929; 1978.

Cells from a poorly differentiated Borrman Type III adenocarcinoma of the stomach of a 70-yr-old man were converted to the ascites form in nude BALB/c mice. The tumor cells were passaged sc in nude mice following removal from the patient. At passage 9, the histology of the cells was similar to that of the original tumor; 10^7 cells were then injected ip into nude mice. The injection resulted in ascites carcinoma with invasion (carcinomatous peritonitis) and liver metastasis. Serial transfers of 1.5×10^5 dispersed cancer cells into the peritoneal cavity of nude mice converted this adenocarcinoma to an ascites form. Hemorrhagic ascites accumulated within 3 wk at the first passage and 4-6 wk in serial passages. Carcinomatous peritonitis occurred consistently in the diaphragm, mesenteries, omentum, and pancreas; metastases were seen in the liver and spleen. Iv injection of 6×10^5 cells at ascites passage 3 into nude mice produced metastatic lesions in the lung and heart. The histology of the invasive and metastatic lesions was similar to that of the original tumor. (8 refs)

8-7116 Relationship Between Gastric Polyps and Gastric Mucosa. (Cze) Mertl, L. (I. vnitrni klinika kulty detskeho lekarstvi, Fakultni nemocnice Pod Peinem, V Uvalu 84, Prague 5, Czechoslovakia); Gregor, O. *Vnitr Lek* 24(9): 842-847; 1978.

he gastric mucosa and gastric secretion were studied in 74 atients with gastric polyps. Malignant (carcinomatous) pops were found in 19 patients, adenomatous polyps in 25, yperplastic polyps in 24, eosinophilic granulomas in 2, fiomas in 2, hemangioma and neurinoma in 1 each. The gasic mucosa was normal in 7 patients with benign polyps; perficial gastritis was found in 10 patients with benign and 2 with malignant polyps, atrophic gastritis in 31 patients ith benign and 10 patients with malignant polyps, and trophic gastritis with metaplasia in 7 patients with benign nd malignant polyps each. Histamine-resistant achlorhydria as found in 38 patients with benign polyps and in 18 patients ith malignant polyps. The findings indicate that chronic flammation is a primary process in the pathogenesis of ucosal polyps, the polyp being a secondary, local manifestaon of gastric mucosa disease. Chronic inflammation also ppears to lead to the development of hyperplastic adenomas. he findings suggest a relationship between alterations in the astric mucosa and tumor growth in the stomach. (24 refs)

8-7117 'Small Intestinal Type' and 'Colonic Type' Intestinal Metaplasia of the Human Stomach, and heir Relationship to the Histogenic Types of Gastric Adenoarcinomas. (Eng) Teglbjaerg, P. S. (Inst. Pathology, Odense Univ. Hosp., DK 5000 Odense, Denmark); Nielsen, H. O. *Acta Pathol Microbiol Scand [A]* 86(5): 351-355; 1978.

he frequency of different histochemical types of intestinal netaplasia (IM) was compared in patients with gastric carinomas of presumed intestinal histogenesis and patients with umors of nonintestinal histogenesis. Operative specimens vere collected from 27 consecutive patients undergoing surgry for stomach cancer. Seven tumors were classified as intesinal cell carcinomas, 6 as pylorocardiac gland carcinomas, 3 as mucous cell carcinomas, and 1 was unclassifiable. Small ntestinal type IM, identified by the staining of goblet cells vith alcian blue pH 2.6-PAS, was present in all 24 stomachs vith IM. Colonic type IM, identified by the reaction of goblet ells with periodate-borohydride/KOH/PAS, was found in cattered IM foci in 11 cases. The frequency of the latter type vas significantly greater in stomachs with tumors of intestiial histogenesis than in those with tumors of nonintestinal istogenesis (ie, intestinal cell carcinomas vs pylorocardiac arcinomas). It is suggested that colonic type IM may have a premalignant potential and that the small intestinal type is merely of a reactive character. (18 refs)

78-7118 Genetic and Communicable Effects on Carcinoembryonic Antigen Expressivity in the Cancer Family Syndrome. (Eng) Guirgis, H. A. (Dept. Preventive Medicine/Public Health, Creighton Univ. Sch. Medicine, Omaha, NB, 68178); Lynch, H. T.; Harris, R. E.; Vandevoorde, J. P. *Cancer Res* 38(8): 2523-2528; 1978.

The potential of plasma carcinoembryonic antigen (CEA) as a discriminant of genetic cancer risk was tested in 272 members of six pedigrees manifesting the cancer family syndrome (CFS) and 191 normal controls. In addition, the role of age and duration of cigarette smoking in CEA expression was quantitated, and connubial effects on CEA levels in this syndrome were determined. The CEA distributions per se were transformed to square root CEA (srCEA) to correct for skewness and kurtosis. Duration of smoking and age showed a positive correlation with srCEA level in both family members and controls. The mean srCEA did not differ between family members and controls of the same smoking status. However, when pedigree data were classified by closeness of relationship to cancer patients, there was a significant linear increase in mean srCEA with increasing genetic cancer risk. Unrelated spouses had mean srCEA levels similar to those for the corresponding risk class of their direct-line mates, and the intraclass correlations of srCEA between direct-line relatives and their spouses approached significance when both spouses were concordant for smoking status. It is suggested that there is a genetic-connubial effect on plasma CEA levels that presumably is due to a common environmental agent acting with the degree of genetic predisposition to cancer. An integrative target cell theory is proposed to explain CEA expressivity in the CFS. The model involves the interaction of the CFS genotype with physical factors (cigarette smoking) and a communicable agent (oncogenic virus). (36 refs)

78-7119 **Peutz-Jeghers Syndrome. Intussusception and Associated Malignancies.** (Fre) Besson, A. (Service de Chirurgie A, 1011 CHUV, Lausanne, Switzerland); Delacretaz, F.; Pescia, G.; Vecerina, S.; Saegesser, F. *Chirurgie* 104(2): 117-130; 1978.

The case histories of six patients representing three families with Peutz-Jeghers syndrome (PJS) are presented. Two of the patients developed cancer and eventually died with multiple metastases. The first patient, a 34-yr-old man, had multiple polyps of the stomach and small and large intestines throughout his life, and he had undergone resection of the jejunum and ilium. At the age of 23, a polyp in the sigmoid colon was invaded by an undifferentiated adenocarcinoma. Ten years later, the patient died of complications following surgery for rectal polyps. Hepatic metastases were observed at this time. The other patient, the mother of two sons with the syndrome, died at the age of 48 with multiple metastases from adenocarcinoma of the uterus. She had the cutaneous symptoms of PJS, and x-rays had shown polyps in the ilium and rectum, but the latter had never given rise to clinical symptoms. The literature reports a 5% incidence of gastrointestinal cancers associated with PJS; 1/6 women with the syndrome develop an ovarian tumor, frequently before age 15. (41 refs)

78-7120 **Chromosomes and B and T Cells in Mycosis Fungoides.** (Eng) Goh, K. (Medical-Oncology Unit, Monroe Community Hosp., 435 E. Henrietta Road, Rochester, NY, 14603); Reddy, M. M.; Joishy, S. K. *Am J Med Sci* 276(2): 197-204; 1978.

Cytogenetic studies were performed using peripheral blood WBC from four male patients (aged 59-78 yr) with mycosis fungoides (MF). The WBC cultures were stimulated with phytohemagglutinin or pokeweed mitogen. Pseudodiploid cells were found in all patients, and they varied between 24% and 42% in each culture. The most consistent chromosomal pattern among the pseudodiploid metaphases was a larger chromosome number 2, the long arm of which appeared longer than that of its homolog. Chromosomal fragments were seen in various proportions in cultures from three patients. The absolute number of lymphocytes from these three patients was lower than that in control cultures. The absolute number of T lymphocytes was also reduced, but only one patient showed a lower proportion of T lymphocytes. Two patients showed a higher frequency but lower absolute number of B cells compared with controls; the frequency and absolute number of B cells were within normal limits in the third patient. The results support the concept that MF is a neoplastic disease, and they suggest that MF and Sezary syndrome are two separate entities. (16 refs)

78-7121 **Pigmented Xerodermoid: First Report of a Family.** (Eng) Hofmann, H. (Universitats-Hautklinik Heidelberg, Vosstrasse 2, D-69 Heidelberg, W. Germany); Schnyder, U. W. *Bull Cancer (Paris)* 65(3): 347-350; 1978.

A family concentration of pigmented xerodermoid, a xeroderma pigmentosum variant, is presented. In a second generation of 13 children, 2 men and 2 women patients had typical clinical signs of xeroderma pigmentosum, including increased pigmentation, strong sunburn reactions, an inordinate number of freckles, solar keratoses, and multiple squamous cell carcinoma of the skin in later life; 3/13 children died in early infancy, and 3 of the 6 remaining siblings died of internal malignancies. Their deceased parents had apparently been normal, as were 22 offspring of this second generation, except for marked sun sensitivity and blistering in 2 sons of one patient. One of these men subsequently died of mammary carcinoma. Of 24 members of the fourth generation, 2 had extensive body freckles, but at an age range of 7-25 no other skin aberrations were so far reported. DNA repair mechanisms were investigated in UV-irradiated lymphocytes and epidermal cells of one of the second generation patients. In these cells, the base-excision repair mechanism was normal but the DNA synthesis time was abnormally long, indicative of pigmented xerodermoid. This appears to be the first report of a family concentration of this condition. (8 refs)

78-7122 **Morphology and Metastatic Nature of Induced Hepatic Nodular Lesions in C57BL x C3H F_1 Mice.** (Eng) Vesselinovitch, S. D. (Dept. Pathology, Pritzker Sch. Medicine, Univ. Chicago, Chicago, IL, 60637); Mihailovich, N.; Rao, K. V. *Cancer Res* 38(7): 2003-2010; 1978.

The metastatic capabilities of well-defined nodular hepatic lesions in mice induced by benzo(a)pyrene (single treatment of 75-150 μg/g), ethylnitrosourea (single treatment of 60-120 μg/g), benzidine-2HCl (continuous treatment of 100 ppm in the diet), and diethylnitrosamine (4 treatments totaling 6-12 μg/g) were evaluated to determine if it is possible to diagnose cancer in the mouse solely by histological examination of the primary lesion. Coded liver and lung tissues from 1,264 treated (C57BL/6J x C3HeB/FeJ)F_1 mice were assessed independently for the presence of primary nodular lesions and metastases, respectively. Primary lesions were classified according to their size, cell morphology, and growth patterns into hyperplastic, adenomatous, and trabecular nodules. None of the 126 mice bearing hyperplastic nodules had pulmonary metastases. Four of 291 mice with adenomatous nodular lesions showed metastases. However, of 733 mice with the trabecular type of nodular lesions, alone or in combination with other lesions, 266 showed pulmonary metastases. The metastases were first detected in mice dying between 51 and 60 wk of age (5%), and the rate increased as a function of age at death, reaching an incidence of 51% in mice surviving >81 wk. It was concluded that nodules showing trabecular and the more anaplastic solid sheet type of growths represented bona fide hepatocellular carcinomas in the mouse. However, before bioassay data of mouse carcinogenesis are interpreted, the nodular lesions should be classified, the experimental conditions fully assessed, and factors modifying hepatocarcinogenesis considered. (23 refs)

78-7123 **Frequency of Occurrence of Hepatocellular Carcinoma in Patients with Porphyria Cutanea Tarda During Long-Term Observation (Meeting Abstract).** (Eng) Kordac, V. (First Medical Clinic, Charles Univ., Prague, Czechoslovakia). *J Clin Chem Clin Biochem* 16(1): 67; 1978. (no refs)

78-7124 **Primary Liver Carcinoma: The Possible Role of Sex Hormones (2 Letters to Editor).** (Dut) Zuidema, P. J. (Amsterdam, Netherlands); Houwert, G. J.; Brandt, K. H.; Bronkhorst, F. B. *Ned Tijdschr Geneeskd* 122(42): 1634; 1978.

Pathologically increased serum alpha-fetoprotein levels were found in 6/14 patients with primary liver carcinoma. Two other patients with mixed hepatocellular-cholangiolar liver carcinoma were negative. (4 refs)

78-7125 **Focal Nodular Hyperplasia of the Liver and Oral Contraceptives.** (Eng) Kinch, R. (Depts.

Obstetrics and Gynaecology, Montreal General Hosp., 1650 Cedar Ave., Montreal, Quebec, Canada H3G 1A4); Lough, J. *Am J Obstet Gynecol* 132(7): 717-727; 1978.

Six cases of focal nodular hyperplasia discovered since 1973 at Montreal General Hospital are presented. Two cases are reported in depth; four were published previously and are summarized. The age of the patients ranged from 21 to 45 yr (four were >40 yr), and all six had taken oral contraceptives for 4-12 yr. Four had taken preparations containing mestranol and one had taken 50 μg ethinyl estradiol + 2.5 norgestrel for 6 yr; the product was unknown in the sixth patient. Each patient had suffered long-term (2-3 yr) upper epigastric discomfort and pain that was mostly located in the area over the hepatic lesion. Upper gastrointestinal series were negative and liver enzyme tests, when performed, were normal. All tumors had the same gross appearance: 3- to 6-cm nodular masses whose resected surface was yellowish and multinodular, with a central fibrous scar radiating into the parenchyma (similar to focal postnecrotic cirrhosis). The normal lobular architecture was replaced by nodules of regenerating parenchyma, with the hepatocytes being arranged in a pseudoacinar pattern. Ductular proliferation was seen along the margins in the vascular stroma. Focal nodular hyperplasia and hepatic adenoma are suggested to be two distinct processes. It is postulated that the estrogen component of the oral contraceptives causes vascular lesions characterized by myointimal hyperplasia and thrombosis, leading to infarct, necrosis, and subsequent nodular hepatic regeneration. Gray-scale ultrasonography is an effective screening method that also aids in a definitive diagnosis. (18 refs)

78-7126 **Liver Cell Adenoma Associated with Oral Contraceptive Hormone Therapy.** (Eng) Nicolaides, N. J. (133 Leichhardt St., Brisbane, Queensland 4000, Australia). *Med J Aust* 2(6): 274-276; 1978.

The case of a 40-yr-old woman who developed a hepatic adenoma in association with 7 yr of oral contraceptive therapy (norethisterone/ethinyl estradiol) is presented. Upon removal of the tumor, widespread interparenchymal hemorrhage was discovered. Catastrophic intraperitoneal hemorrhage could well have eventuated had the capsule been breached, and needle biopsy of such a lesion may have proved disastrous. (29 refs)

78-7127 **A Close Association of Hepatocellular Carcinoma with Cirrhotic Changes Among 275,857 Pathological Autopsy Cases in Japan During 16 Years from 1958 to 1973.** (Eng) Miyaji, T. (Japanese Inst. Pathology, Osaka 530, Japan). *Kurume Med J* 24(Suppl): S63-S79; 1977.

The association between hepatocellular carcinoma (HCC) and cirrhotic changes was studied based on 275,857 autopsy cases registered in Japan during 1958 through 1973. The most frequent malignancy was gastric carcinoma, followed by leukemia, bronchogenic carcinoma, and HCC. During the 16-yr period, 7,002 HCC's and 15,136 cases of cirrhotic changes not associated with HCC or cholangiocellular carcinoma were registered. A gradual increase in HCC'S, especially in men, was noted. Seventy percent of the HCC's in men and 53.3% of those in women were associated with cirrhosis, as were 20.7% of cholangiocellular carcinomas in men and 10.7% of those in women. Liver fibrosis was associated with HCC in 1.6% of affected men and 2.0% of the women and with cholangiocellular carcinoma in 8.7% of affected men and 22.0% of the women. Of the cirrhoses associated with HCC, 85.8% of those in men and 80.8% of those in women were either unspecified (US) cirrhosis or the Nagayo-Miyake B-type (posthepatic or macronodular) cirrhosis. Among the cirrhoses not associated with carcinoma, 50.0% in men and 44.7% in women were of the B and US types. A'-type cirrhosis (transitional between postnecrotic and B type) and B'-type cirrhosis (transitional between fibrosis and B type) were assoicated with HCC in 29.7% and 23.2% of men, respectively, and in 20.7% and 21.5% of women. The number of postnecrotic and A'-type cirrhoses associated with HCC tended to increase over the 16-yr interval. The peak of HCC in men and women was at 55 yr and that of B type and US cirrhosis was at 60 yr. (66 refs)

78-7128 **The Histiocytic Origin of the Multinucleated Giant Cells in Myeloma Kidney.** (Eng) Factor, S. M. (Dept. Pathology, Albert Einstein Coll. Medicine, Bronx, NY); Winn, R. M.; Biempica, L. *Hum Pathol* 9(1): 114-120; 1978.

The cellular origin of the syncytial multinucleated giant cells in a patient with myeloma kidney disease was determined by light and electron microscopy (EM) and by immunofluorescence. The patient was a 71-yr-old black man with uremia and dysphagia. Even though renal tissue was not fixed for >20 hr after the patient's death, the multinucleated giant cells appeared well-preserved, contrasting with the marked degeneration of the tubular epithelium (TE). There was a consistent correlation between the presence of giant cells around tubular casts and breaks in the basement membrane. Although casts were present within Bowman's space, they were never associated with giant cells, possibly because the parietal glomerular basement membrane is relatively resistant to penetration by inflammatory cells. One possible source of misinterpretation of a direct transition between the giant cells and the TE was noted by light and EM. Degenerated TE was frequently found in close apposition with giant cells or, in some instances, within spaces enclosed by giant cell cytoplasmic processes. However, EM showed that there was no fusion of cell membranes. There was also a clear difference in staining reactions and a sharp delimitation of cell contours between the giant cells and the TE when the renal tissue was stained for reticulin fibers. Immunofluorescence studies suggested that the multinucleated giant cells phagocytose fragments of proteinaceous casts. The histiocytic origin of the

giant cells was confirmed directly by EM; a lock and key configuration, numerous mitochondria, large numbers of membrane-bound structures, dense bodies, numerous cytoplasmic vesicles, and luminal projections of the plasma membrane were present. It is concluded that the giant cells arise in the interstitial tissues, migrate through breaks in the tubular basement membrane, and engulf and surround intratubular protein casts. (23 refs)

78-7129 **An Unusual Osteosclerotic Metastasis to the Calcaneus in Basal-Cell Adenocarcinoma of the Kidney in a Child.** (Cze) Mrzena, V. (Ortopedicka klinika, Fakulta detskeho lekarstvi KU, Karlovo nam. 1, 128 00 Prague 2, Czechoslovakia); Belikova, H. *Acta Chir Orthop Traumetol Cech* 45(3): 214-216; 1978.

Osteosclerotic metastasis to the calcaneus was the first symptom of a kidney tumor in a 13-yr-old boy. Basal-cell adenocarcinoma of the kidney was found at surgery. (5 refs)

78-7130 **Filiform Polyposis.** (Eng) Zegel, H. G. (Dept. Radiology, Hosp. Univ. Pennsylvania, 3400 Spruce St., Philadelphia, PA, 19104); Laufer, I. *Radiology* 127(3): 615-619; 1978.

Filiform polyposis presents a characteristic radiographic appearance of long, filamentous filling defects in an otherwise normal colon. It has been documented in patients with a prior history of ulcerative or granulomatous colitis. In addition, a solitary filiform polyp was discovered in a patient with previously undiagnosed inflammatory bowel disease, and in a patient with Crohn's disease involving the small bowel. Filiform/polyposis may represent a nonspecific sequela of diffuse mucosal inflammation, and it should not be mistaken for a neoplastic form of polyposis. (5 refs)

78-7131 **Cell Proliferation of the Colorectal Mucosa in Normal Subjects and Patients with Preneoplastic or Neoplastic Pathology of the Colon and Rectum.** (Fre) Maskens, A. P. (Unite de Recherche Cancerologique, Clinique Saint-Michel, Rue de Lantsheere 19, B-1040 Brussels, Belgium). *Acta Gastroenterol Belg* 41(5/6): 226-240; 1978.

Proliferation of cells in the colorectal mucosa was studied by radioactive thymidine uptake in samples from 25 patients (26-71 yr of age; av age 54 yr) with intestinal polyps (14 adenomatous, 9 hyperplastic, 2 villous) and in samples of normal mucosa of 5 tumor-free subjects and 11 patients with colorectal cancer. Distribution of radioactivity was graphed for the lower, middle, and upper thirds of the glandular epithelium in normal and pathological mucosa. In mucosa from normal patients, 66.3% of the radioactivity was recovered in the lower third, 33.5% in the middle third, and 0.3% in the upper third. In mucosa samples of normal appearance from the cancer patients, 57.7% of the radioactivity was recovered in the lower third, 39.4% in the middle third, and 3.0% in the upper third. In mucosa samples from hyperplastic polyps 40% of the radioactivity was recovered in the lower third, 93.5% in the lower two-thirds, and 7.5% in the upper third. The location of radioactivity was difficult to calculate exactly in samples from adenomatous polyps due to the morphology and size of the glands; however, av uptake was elevated (23.1% compared with 8.3%) toward the surface regions. Only two samples from villous polyps were analyzed for radioactivity, and the fragile villi made counting difficult. (32 refs)

78-7132 **The Background Processes in the Development of Endometriosis and Endometrioid Cancer of the Ovaries.** (Rus) Kolosov, A. E. (N. N. Petrov Res. Inst. Oncology, USSR Ministry Health, Leningrad, USSR). *Vopr Onkol* 24(3): 44-50; 1978.

Surgical specimens from 87 patients with ovarian endometriosis and 23 patients with endometrioid carcinoma of the ovaries were analyzed morphologically to determine the changes or background processes leading to these conditions. The group included 61 pre- and 49 menopausal patients. The background lesions included microfollicular cysts (54 patients) and hyperplasia of the ovarian stroma (73 patients: 22 with diffuse, 37 with focal, and 14 with mixed hyperplasia). The premenopausal patients had predominantly follicular cysts and focal hyperplasia, but the menopausal patients had diffuse hyperplasia. Hyperplasia of the endometrium was diagnosed in 41 patients. (16 refs)

78-7133 **Laurence-Moon-Bardet-Biedl Syndrome and Endometrial Carcinoma.** (Ger) Peiker, G. (Frauenklinik, Friedrich-Schiller-Universitat, Bachstr. 18, DDR-69 Jena, E. Germany); Bohm, W.; Carol, W. *Zentralbl Gynaekol* 100(17): 1126-1130; 1978.

Laurence-Moon-Bardet-Biedl syndrome associated with Stein-Leventhal syndrome and polycystic ovaries was diagnosed in an 18-yr-old obese woman with irregular monophasic menstrual cycles. Endometrial adenocarcinoma was found 5 yr later. Compared with normal values, the total estrogen excretion in the urine was increased (43 μg/24 hr), and the 17-ketosteroid excretion was low (2 mg/24 hr). The genesis of the endometrial adenocarcinoma can be explained by the extraglandular (peripheral) aromatization of androgens into estrogens, especially by the transformation of androstenedione into estrone and the absence of estradiol and progesterone during the long-term exposure of the endometrium to estrone. (9 refs)

78-7134 **Choriocarcinoma with Metastasis in a Postmenopausal Woman.** (Eng) Dougherty, C. M. (Louisiana State Univ. Sch. Medicine, LSU Unit, 5825 Airline Highway, Baton Rouge, LA, 70805); Cunningham, C.; Mickal, A. *Am J Obstet Gynecol* 132(6): 700-701; 1978.

The case of a black woman who had a 34-yr latent period between her last pregnancy (at age 52) and subsequent metastatic choriocarcinoma (ChC) is described. Amenorrhea began after her last pregnancy. Molar remnants, including hydropic villi, retained within the uterus for possibly 34 yr furnished proof of primary trophoblastic neoplasia. Viable, growing ChC in the lungs at autopsy proved the malignant potential of the tumor. (4 refs)

78-7135 **Primary Adenocarcinoma of the Vagina: A Case Report with Light and Electron Microscopic Study.** (Eng) Navas Palacios, J. J. (Dept. Anatomic Pathology, Ciuidad Sanitaria de la Seguridad Social "1 de Octubre,", Carretera de Andalucia, km. 5.4, Madrid 26, Spain); de Agustin de Agustin, P. P.; Martinez Tello, F. J. *Acta Cytol (Baltimore)* 22(5): 358-361; 1978.

The case of a 46-yr-old woman with primary vaginal adenocarcinoma unrelated to hormone therapy is reported, and the results of histological and ultrastructural studies are presented. The patient presented with vaginal bleeding after intercourse, and, on examination, an exophytic necrotic mass was found to fill most of the vagina. After removal of the vaginal content, the cervix appeared unremarkable; a 6-cm implantation area was noted on the posterior vaginal wall and fornix. The presence of a primary site other than the vagina was ruled out by lower gastrointestinal tract and chest x-rays, laparoscopy, and rectosigmoidoscopy. The pathologic diagnosis of primary adenocarcinoma of the endometrioid subgroup was made. The ultrastructural features were different from those of clear cell-type vaginal adenocarcinoma. Glycogen aggregates were absent, and the rough endoplasmic reticulum was sparse and did not form stacks. Endocervical type adenocarcinoma was ruled out because of the absence of characteristic mucinous secretory granules. The ultrastructore of the mesonephric nests was different from that of tumors with a true mesonephric origin. The ultrastructural features of renal cell carcinoma were also absent in this case. Because of the ultrastructural features of normal endometrium and endometrial adenocarcinoma are similar to the observations in the present case, it is concluded that the adenocarcinoma was of mullerian origin. (27 refs)

78-7136 **Viral Particles in Cervical Condylomatous Lesions.** (Eng) Della Torre, G. (Divisione di Oncologia Sperimentale A., Istituto Nazionale Tumori, Via G. Venezian 1, 20133 Milan, Italy); Pilotti, S.; de Palo, G.; Rilke, F. *Tumori* 64(5): 549-553; 1978.

Koilocytosis is a pathologic alteration of squamous epithelial cells of the uterine cervix that is characterized by small nuclei with an indented outline and clumped chromatin surrounded by a halo of transparent cytoplasm. Biopsy specimens from eight patients with condylomatous lesions of the uterine cervix were examined histologically and ultrastructurally. Cervical smears showed koilocytotic atypia in varying numbers of cells in all cases, and malignant epithelial tumor cells were found in one case. In seven cases, the colposcopic pattern was that of early condylomatosis; one case was colposcopically negative except for a small leukoplakia. Ultrastructural examination demonstrated many intranuclear viral particles morphologically identical to papovavirions in the koilocytotic epithelial cells of four patients. The particles were also identical to those of the papilloma virus found in genital condylomata acuminata, suggesting that cervical condylomatous lesions are related etiologically to condylomata acuminata. (8 refs)

78-7137 **Early Vulvar Carcinoma.** (Eng) Kunschner, A. (Dept. Obstetrics and Gynecology, Magee-Womens Hosp., Univ. Pittsburgh, Pittsburgh, PA, 15213); Kanbour, A. I.; David, B. *Am J Obstet Gynecol* 132(6): 599-606; 1978.

Fifty-eight cases of early vulvar neoplasia recorded in Tumor Registry at Magee-Womens Hospital during 1947-1976 were reviewed. There were 23 cases of squamous cell carcinoma in situ; 16 cases of carcinoma in situ with microinvasion, and 19 cases of occult carcinoma. All these cases were treated surgically with the modality varying from local excision to radical vulvectomy with inguinal lymph node dissection. Regardless of the surgical therapy, none of the patients died of the vulvar malignancy. As part of routine gynecologic surveillance, more critical attention should be given to examination for early epithelial neoplastic lesions of the vulva. This can be accomplished by simple inspection and the use of special diagnostic aids. Biopsy specimens should be reviewed histologically for depth of invasion and the treatment individualized to the patient, with considerations for conservation, especially in younger women. (16 refs)

78-7138 **Neoplastic Potential of the Dysgenetic Gonad. Case Report.** (Eng) Fayez, J. A. (Truman Medical Center, 2301 Holmes, Kansas City, MO, 64108); Jonas, H. S.; Masterson, B. J. *Mo Med* 75(11): 564-566; 1978.

The case of a 16-yr-old girl with a 46/XY karyotype in whom bilateral gonadoblastoma developed in the gonadal streaks is presented. Gonadal dysgenesis was diagnosed on the basis of the patient's karyotype and lack of secondary sex characteristics. An infantile uterus was found at laparotomy, and streak gonads were identified in the position of normal ovaries. Biopsy disclosed gonadoblastoma, and a total hysterectomy and bilateral salpingogonadectomy were performed. This case il-

lustrates the malignant potential of the dysgenetic gonad. (10 refs)

78-7139 **Carcinoma In Situ of the Bladder. Report of 10 Cases.** (Fre) Steg, A. (Clinique Urologique, Hopital Cochin, 27 rue du Faubourg Saint-Jacques, 75674 Paris Cedex 14, France). *Ann Urol (Paris)* 12(2): 73-82; 1978.

The symptoms, diagnosis, and therapeutic aspects of carcinoma in situ (CIS) of the urinary bladder are described, and the histology and significance of CIS for invasive carcinoma are discussed in connection with 10 cases of CIS (9 men, 1 woman, aged 51-74 yr). No occupational carcinogenic factors were found. Differentiation between CIS and dysplasia is often very difficult. In simple dysplasia, the number of cell layers is increased. In atypical dysplasia of the epithelium, this change is also associated with nuclear anomalies, while the lack of cohesion and maturation, and giant cells are characteristic of CIS. It is a well-established fact that CIS can evolve into invasive carcinoma; such transformation is seen in 20-50% of all cases, and takes place in 1-6 yr after the diagnosis of CIS. Each invasive carcinoma of the urinary bladder in the 10 patients had a CIS stage. (23 refs)

78-7140 **Natural History of Papillary Lesions of the Urinary Bladder in Schistosomiasis.** (Eng) Kuntz, R. E. (Dept. Parisitology, Southwest Foundation Res. and Education, San Antonio, TX, 78284); Cheever, A. W.; Bryan, G. T.; Moore, J. A.; Huang, T. C. *Cancer Res* 38(11, part 1): 3836-3839; 1978.

Attempts to autologously and heterologously transfer bladder lesions in monkeys (*Cebus apella*) infected with *Schistosoma haematobium* (1,000 or 2,000 cercariae) are reported, along with the natural history of papillary transitional cell lesions in these animals. The animals were examined by laparotomy and cystotomy 94-164 wk postinfection, and six were chosen for autologous transplant studies, three for heterologous transplant studies. These animals were followed for 14-136 wk postcystotomy and then subjected to necropsy. At cystotomy, variable epithelial hyperplasia was observed in the urinary bladder of the nine monkeys. All biopsy specimens showed marked *S. haematobium* infection. At necropsy, involution of the urothelial hyperplasia had occurred in 8/9 monkeys; the only monkey in which the hyperplasia persisted was also the only monkey with marked active infection. No growth of transplanted epithelium was evident by palpation or by gross or microscopic examination. The results indicate that proliferative transitional cell lesions have restricted growth potential. (15 refs)

78-7141 **Desmosome Ultrastructure and the Biological Behavior of Chemical Carcinogen-induced Urinary Bladder Carcinomas.** (Eng) Pauli, B. U. (Dept. Patholo gy, Rush Medical Coll., 1753 W. Congress Parkway, Chica go, IL, 60612); Cohen, S. M.; Alroy, J.; Weinstein, R. S *Cancer Res* 38(10): 3276-3285; 1978.

The relationship between desmosomes and tumor invasive ness was studied in urinary bladder transitional cell car cinomas induced in male Fischer rats b N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (0.2% of die for 26 wk). The number of desmosomes per unit area of plas ma membrane was significantly reduced in the carcinomas However, the percentage of cell surface area occupie by desmosomes were greater in carcinomas than i controls. This was accounted for on the basis of in creases in desmosomal size, which result from squamou differentiation within the tumors. Areas of transitiona cell differentiation and squamous differentiation demon strated an equal capacity for invasiveness. Desmosome were abundant in invading nests of tumor cells. Thes findings argue against the idea that decreased inter cellular adhesion is a prerequisite for tumor invasion since strong interadhesion is probably a function o the area occupied by the intercellular junctions. (48 refs.)

78-7142 **On the Etiology of Cancer of the Prostate** (Eng) Stein-Werblowsky, R. (Bikur Cholim Hosp., POB 492, Jerusalem, Israel). *Eur Urol* 4(5): 370-373 1978.

Experiments demonstrating that the penetration of spermatozoa into the prostatic tissue of Wistar rats can cause abscesses, lithiasis, and carcinoma are presented. Nine of 20 animals developed one of these lesions following the injection of 0.1-0.2 ml of autologous sperm or homologous sperm into the anterior prostate at its junction with the neck of the bladder. (11 refs)

78-7143 **On the Etiology of Testicular Tumors. An Experimental Study.** (Eng) Stein-Werblowsky, R. (Bikur Cholim Hosp., Jerusalem, Israel). *Eur Urol* 4(1): 57-59; 1978.

The etiology of testicular tumors was examined in Wistar rats. One testicle was extirpated and minced, and 0.2 ml of the resulting suspension was injected into the other testicle. Four of 10 rats developed testicular abnormalities within 32-47 days after injection. One rat had a tumor filling the whole abdomen; the testicle was not enlarged and the tumor, which was readily transplantable to homologous recipients, was apparent only on histological examination of the testis. The testicle of another rat was greatly enlarged, and normal tissue was wholly replaced by tumor. No distant metastases were observed, but the animal died of local spread 3 wk after orchiectomy. These results demonstrate that testicular tumors can develop rapidly as a result of autofertilization. It

possible that mature, motile spermatozoa, instead of being scharged into the lumen of the seminiferous tubuli, penetate the cells of the germinal epithelium. These results also oint to a possible mechanism common to all carcinogenic rocesses, that of fertilization in the sense of nuclear fusion. he function of a carcinogenic agent may be the promotion f nuclear fusion. The chromosome abnormalities, such as xcess of chromatin material and aneuploidy generally associated with cancer, lend further support to this hypothesis. refs)

3-7144 **Measurement of Urinary Epinephrine in Screening for Pheochromocytoma in Multiple ndocrine Neoplasia Type II.** (Eng) Hamilton, B. P. (Dept. Iedicine, Veterans Admin. Hosp., 3900 Lock Raven Blvd., altimore, MD, 21218); Landsberg, L.; Levine, R. J. *Am J Ied* 65(6): 1027-1032; 1978.

sensitive screening test for the pheochromocytoma compoent of multiple endocrine neoplasia type II (MEN-II), comarable to the calcitonin radioimmunoassay for medullary arcinoma of the thyroid (MCT), has been lacking. A large mily with MEN-II was screened for pheochromocytoma by easuring 24-hr urinary catecholamines as norepinephrine nd epinephrine fractions. Pheocromocytomas had been conrmed at surgery in six family members and at autopsy in ne. All seven have had associated MCT. In an additional x family members, only MCT has been detected. In 5/6 atients treated surgically, the urinary epinephrine fraction as the dominant or sole abnormality, and an epinephrine evel >20 μg/24 hr, was diagnostic of pheochromocytoma. n increased urinary epinephrine fraction appears to be a haracteristic feature of MEN-II pheochromocytomas, and easurement of this fraction a sensitive and reliable screening st in afflicted families. (16 refs)

78-7145 **Seminoma in a 12-Year-Old Male with 46 XY/45 XO Karyotype.** (Eng) Doll, D. C. (Dept. Medicine, West Virginia Univ. Medical Center, Morgantown, WV, 26506); Kandzari, S.; Jenkins, J. J.; Amato, S.; Jones, B. *Cancer* 42(4): 1823-1825; 1978.

The case of a 12-yr-old boy with pure seminoma in an undecended testis and 46 XY/45 XO karyotype is presented. The resence of the undescended testicle may have been a predisposing factor in the development of the malignancy. The abormal chromosome constitution might have been an isolated inding with no relation to the patient's malignancy. However, it is possible that the abnormal karyotype was a contributng factor in both the undescended testicle and seminoma. (17 efs)

78-7146 **Gonadal Tumors in Testicular Dysgenesis Syndrome.** (Rus) Bronshtein, M. E. (Lab. Pathologic Anatomy, Inst. Experimental Endocrinology and Chemistry Hormones, Moscow, USSR); Iur'eva, N. P.; Golubeva, I. V. *Probl Endokrinol (Mosk)* 24(2): 30-35; 1978.

Of 84 patients (1.5-39 yr of age) with testicular dysgenesis syndrome, 26 had gonadal tumors. These tumors were diagnosed in only two patients at clinical examination; the rest were diagnosed at laparotomy. Tumor size ranged from 1.5 x 0.8 cm to 12 x 8 x 7 cm. Of the 26 patients, 10 had both testicles located either in the abdomen (9) or in the inguinal canal (1); 6 of the former had tumors of both gonads. Histologically, the tumors were classified as gonadoblastomas (18) or dysgerminomas (8). (11 refs)

78-7147 **Malignant Transformation of Osteoid Osteoma.** (Ger) Wahl, H. (Orthopadische Klinik, Medizinische Akademie Magdeburg, Schellingstrasse 3/4, DDR-301 Magdeburg, E. Germany); Dominok, G. W. *Zentralbl Chir* 103(22): 1490-1492; 1978.

An osteoid osteoma of the left tibia was diagnosed and partially resected in a 22-yr-old woman 3 yr after onset of the first symptoms. The symptoms (pain, swelling, and local hyperthermia) recurred 3 mo later. An osteosarcoma of the same site was diagnosed following partial resection performed about 2 yr after the first operation. To date, she remains free from any metastasis. (6 refs)

78-7148 **Tissue Culture Studies on Human Giant Cell Tumor and Osteosarcoma.** (Eng) Ishii, S. (Dept. Orthopaedic Surgery, Hokkaido Univ. Sch. Medicine, Kita-14-jo, Nishi-5-Chome, Sapporo, Hokkaido, Japan); Yamawaki, S.; Sasaki, T.; Usui, M.; Ubayama, Y.; Minami, A.; Yagi, T. *Int Orthop* 2(1): 77-86; 1978.

The cytological aspects of giant cell tumors (GCT) and osteosarcomas (OS) were investigated in vivo and in vitro. Primary cultures of GCT were successful in 33/41 trials, and 34/33 were transferred serially for more than two subculture passages. Two established lines (G-1 and G-2) were maintained for long-term cultivation. Primary OS cultures were successful in only 22/61 trials, and none of the cultures survived >10 passages. Although round at initial cultivation, the giant cells became fibroblastlike after several hours; after 8-10 mo of cultivation, G-1 and G-2 became epitheliallike. The ultrastructure of the giant cells became increasingly complex with time in culture, displaying numerous microvilli, well-developed organelles, and free ribosomes, but the ultrastructure of the OS cells in primary culture

was essentially the same as that of the in vivo tumor cells. The GCT began with a normal chromosome complement of 46 and a superficially normal diploid karyotype. In contrast, the OS were characterized by aneuploid modal numbers. The number of polyploid and aneuploid cells in the GCT increased with passage number, resulting in a modal chromosome number of 65 at subculture 325. The lactate dehydrogenase (LDH) isozyme patterns of the GCT showed max activity in fractions IV and V; those of the OS showed max activity in fraction III. The LDH isozyme patterns of G-1 and G-2 showed max activity in fractions III and IV, respectively. In later transfer generations, G-1 and G-2 produced, in Wistar/Mk rats, tumors by sc inoculation and tumor death by iv inoculation. Sarcomatous stromal cells in the sc tumors were enmeshed in the hyaline network, resulting in the formation of osteoid or chondroid tissue. The results strongly suggest that the benign GCT may have become malignant during the long in vitro transfer period. (15 refs)

See also:
*(Rev.): 78-6605, 78-6610, 78-6612, 78-6616, 78-661
78-6624, 78-6626, 78-6639, 78-6645, 78-665
78-6652, 78-6686, 78-6687, 78-6689, 78-669
78-6695, 78-6700, 78-6703, 78-6705, 78-670
78-6707, 78-6708.
*(Chem.): 78-6712, 78-6713, 78-6715, 78-672
78-6723, 78-6728, 78-6729, 78-673
78-6739, 78-6742, 78-6744, 78-675
78-6757, 78-6765, 78-6776, 78-678
78-6786, 78-6789, 78-6790, 78-679
78-6797, 78-6798, 78-6801.
*(Phys.): 78-6809, 78-6810, 78-6814, 78-682
78-6831, 78-6832, 78-6836.
*(Viral): 78-6858, 78-6862, 78-6875, 78-6899, 78-691
78-6929, 78-6934, 78-6948, 78-6952, 78-695
78-6958, 78-6961, 78-6962, 78-6977.
*(Immun.): 78-6980, 78-7035, 78-7036, 78-706
*(Epid.-Biom.): 78-7152, 78-7153, 78-7154, 78-716

3-7149 **Chronic Dental Infections in the Etiology of Glioblastomas (Meeting Abstract).** (Eng) Storbecker, P. (Akerbyvagen 282, Taby/Stockholm, Sweden). *Neuropathol Exp Neurol* 37(5): 695; 1978. (1 ref)

8-7150 **Proliferative State of Blast Cell Progenitors in Acute Myeloblastic Leukemia (AML).** (Eng) Minden, M. D. (Ontario Cancer Inst., 500 Sherbourne St., Toronto, Ontario M4X 1K9, Canada); Till, J. E.; McCulloch, E. A. *Blood* 52(3): 592-600; 1978.

Blast cell colony formation by WBC from the peripheral blood of 15 patients with acute myeloblastic leukemia was studied. Colony formation by WBC from these patients was influenced markedly by the concentration of media conditioned by the leukocytes (LCM) in the presence of phytohemagglutinin (PHA). At low PHA LCM concentrations, colonies were compact, immobile, and situated at the bottom of the culture dishes. At higher PHA LCM concentrations, colonies were larger and globular in shape, and they floated in the methylcellulose. The former colony morphology was usually associated with peroxidase-negative cells of blastlike morphology that did not form erythrocyte (E) rosettes. Colonies at high PHA LCM concentrations were composed of small cells (resembling normal lymphocytes) that readily formed E rosettes. The major finding is that progenitors of blast cell colonies are predominantly in a rapid cell cycle, as judged by determinations of the proportion of the cycle in the S phase using tritiated thymidine or hydroxyurea as a DNA synthesis-specific inhibitor. Unless there are very unusual distributions of the cells around the cell cycle, the data indicate that the population of cells detected by this assay is rapidly proliferating. The culture assay for blast cell progenitors detects a minority cell population of morphologically identified blasts; this subpopulation has sufficient proliferative potential for colony formation. The observation that blast progenitors are rapidly proliferating is consistent with the view that they serve to maintain the rest of the blast population. (36 refs.)

78-7151 **The Association between Bronchial Cancer Mortality and the Tobacco Industry in Switzerland between 1970 and 1975.** (Fre) Cardis, F. (Lausanne, Switzerland). *Broncho-Pneumologie* 28(1): 29-30; 1978.

Between 1970 and 1975, bronchial cancer mortality in Swiss women increased 41.5%, vs only 27.8% for Swiss men. During this time, mortality due to other malignant tumors decreased 8.91% in men but increased 3.62% in women, and mortality from all malignant tumors increased by 13.34% in men and 4.74% in women. The increase in bronchial cancer mortality in women may have been the result of an increase in the number of women smoking cigarettes. (no refs.)

78-7152 **Nasopharyngeal Cancer in Sabah: Statistics, Observations and Personal Experiences (Meeting Abstract).** (Eng) Kulkarni, M. G. (Queen Elizabeth Hosp., Kota Kinabalu, Sabah, Malaysia). *In: Summary Program and Abstracts of Papers. Proceedings of the 3rd Asian Cancer Conference Held by the Phillipine Cancer Society under the Auspices of the Asian Federation of Organizations for Cancer Research and Control in Manila, 26-30 September, 1977.* Philippine Cancer Society. (Manila, Philippines): 184 pp.; 64-65; 1977. (no refs)

78-7153 **Perspective of Cancer in Iran (Meeting Abstract).** (Eng) Habibi, A. (Dept. Pathology, Tehran Univ., 32 Churchill Ave., Tehran, Iran). *In: Summary Program and Abstracts of Papers. Proceedings of the 3rd Asian Cancer Conference Held by the Philippine Cancer Society under the Auspices of the Asian Federation of Organizations for Cancer Research and Control in Manila, 26-30 September, 1977.* Philippine Cancer Society. (Manila, Philippines): 184 pp.; 85-86; 1977. (no refs)

78-7154 **Celiac Disease. II. Differences in Its Course in Survivors and Deceased Subjects, and Tumor Incidence.** (Cze) Dvorak, M. (Interni oddeleni fakultni polikliniky, Karlovo nam. 32, 121 11, Prague 2, Czechoslovakia); Fric, P.; Lojda, Z. *Cesk Gastroenterol Vyz* 32(4): 217-226; 1978.

Thirty-two adults with celiac disease were followed from 1955 to 1975. Thirteen of the 32 patients died. Cardiopulmonary disease was the cause of death in six cases, suicide in one and malignant tumors in six. The tumors included malignant lymphomas (4), bronchogenic carcinoma (1), and gynecological carcinoma (1). One of the survivors developed jejunal adenocarcinoma, which was successfully resected. The tumors were considered to be a late complication of prolonged celiac disease. Gluten-free diets reduced the cancer risk only partly. (18 refs)

78-7155 **Lung Cancer Mortality in Uranium Miners (Methodological Aspects) (Letter to Editor).** (Eng) Kunz, E. (Inst. Hygiene and Epidemiology, Centre Radiation Hygiene, 100 42 Prague 10, Czechoslovakia); Sevc, J.; Placek, V. *Health Phys* 35(4): 579-580; 1978.

Data from a 1976 epidemiological study of lung cancer mortality in Czech uranium miners were reevaluated for a group of miners entering employment in 1948-1952. The mortality experience was analyzed in terms of number of cases per unit time at risk, which began with entry into the study group and ended at the cut-off date of the analysis. The results of this recalculation show a coincident picture of response to the increase of cumulative exposure, as in the earlier evaluation. Significant differences between observed and expected values of lung cancer were found in all exposure categories with the exception of the lowest one. The differences in the frequency of additional cases among exposure categories were also significant and, contrary to a study on American uranium miners, confirmed the increase in lung cancer incidence in relation to dose from the first category of exposure upward. The recalculation led to some increase in the estimated number of additional cases in higher exposure categories and a decrease in lower categories compared with the earlier treatment. The distortions caused by the earlier method, however, are not large because the Czech miners entered work and exposure in the same relatively narrow 5-yr period and reached the final exposure levels mostly in the first 5 yr of work. (4 refs)

78-7156 **Lung Cancer on a Nickel Smelting Island (Meeting Abstract).** (Eng) Reed, D. (California State Health Dept., Berkeley, CA, 94704); Lessard, R.; Maheux, B. *Am J Epidemiol* 108(3): 233; 1978. (no refs)

78-7157 **Current Vital Statistics: Methods and Interpretation.** (Eng) Adelstein, A. M. (Office Population Censuses and Surveys, London WC2B 6JP, England). *Br Med J* 2(6143): 983-987; 1978.

Statistical analyses of mortality rates in England and Wales show a sharp rise in lung and bronchial cancer deaths among women aged >45 yr and, since 1961, a moderate decline in the rates among men. Differences in smoking habits may account for some of the differences in mortality among men of different social classes. Proportional mortality rates for stomach, intestinal, and rectal cancer are lower than expected among immigrants from India, with Asians having even lower rates than Indian-born Britons. (9 refs)

78-7158 **Incidence of Bilateral Tumours in a Population-based Series of Breast-Cancer Patients. I. Two Approaches to an Epidemiological Analysis.** (Eng) Prior, P. (Birmingham Regional Cancer Registry, Queen Elizabeth Hosp., Birmingham, England); Waterhouse, J. A. *Br Cancer* 37(4): 620-634; 1978.

The incidence of second primary breast tumors in the contralateral breast was determined among 21,967 primary breast cancer patients registered with the Birmingham Regional Cancer Registry between 1936 and 1964. The results were based on >90,000 woman-years at risk and 399 second primary tumors. When the data were analyzed by a method that included coincidental tumors, the overall risk of a tumor in the contralateral breast was found to be 3.0 times that of a first primary in the general population. The corresponding risks for the three main age groups (at time of diagnosis of first primary tumor) were 5.6 (15-44 yr), 3.7 (45-59 yr), and 1.8 (≥60 yr). When coincidental tumors were excluded from the analysis, the relative risk was found to be 2.4 overall and 5.3, 3.0, and 1.0 for the respective age groups. The level of risk was negatively correlated with age at first primary, and the relative risk remained fairly constant over time. (11 ref

78-7159 **Carcinoma of the Breast in Women under th Age of 30 (Letter to Editor).** (Eng) Logan, C J. (Ulster Hosp, Dundonald, Down, England). *Br Med* 2(6143): 1023; 1978.

Of a group of 213 breast cancer patients, only 3 were <3 yr old, vs 10 of a previously reported group of 195 patients a high incidence for this age group. Malignancy was discovered in the three women only upon biopsy. None has developed metastases after several years. (1 ref)

78-7160 **Carcinoma of the Breast in Women under th Age of 30 (Letter to Editor).** (Eng) Jones, V (Radiotherapy Center, Velindre Hosp., Cardiff, Wales); Slater, A. *Br Med J* 2(6174): 1300; 1978.

Assessment of the age distribution of breast carcinoma patients referred to a radiotherapy center from 1955 to 197 showed that the age incidence had not changed markedly during this period. The number of women <30 yr old presenting with breast cancer remained at ≤1.1%. (no refs)

78-7161 **Tubular Carcinoma of the Breast. A Study of Frequency.** (Eng) Carstens, P. H. (Dept. Pathology, Univ. Louisville Sch. Medicine, P.O. Box 35260, Louisville, KY, 40232). *Am J Clin Pathol* 70(2): 204-210; 1978.

The frequency of tubular carcinoma of the breast among 409 infiltrating breast carcinomas diagnosed during 1974 in the Louisville, Kentucky, area was determined. This carcinoma was histologically defined as an infiltrating breast cancer con-

sisting of tubular structures separated by an abundant amount of hyalinized stroma. A total of 42 tubular carcinoma cases were identified in women aged 26-84 yr. Five patients had bilateral breast cancer, and in three, the contralateral breast also contained tubular carcinoma. Two patients had multifocal tubular carcinoma. Axillary lymph nodes were available for examination with 36/42 breast specimens, and metastatic foci were found in 6. Three histological types of tubular carcinoma were identified: (1) sclerosing type, characterized by a haphazard arrangement of tubules infiltrating into surrounding fat and connective tissue; (2) pure type, consisting of desmoplastic hyalinized stroma surrounding a few tubular structures; and (3) mixed type, in which at least 75% of the tumor was of the tubular variety. Five patients had the first type (none had involved lymph nodes), 9 had the second type (1 with involved nodes), and 28 had the third type (5 with involved nodes). All 42 patients are alive 2 yr after diagnosis; 2 patients have had recurrences. These findings suggest that this type of breast cancer is not as rare as previously reported. (9 refs.)

78-7162 **The Hormonal Basis of Breast Cancer: Elevated Plasma Levels of Estrogen, Prolactin, and Progesterone.** (Eng) Henderson, B. E. (Dept. Pathology, Univ. Southern California, Los Angeles, CA, 90033); Pike, M. C.; Gerkins, V. R.; Casagrande, J. T. *In: Incidence of Cancer in Humans. Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation.* Hiatt, H. H.; Watson, J. D.; Winsten, J. A., eds. (Cold Spring Harbor: Cold Spring Harbor Laboratory): Origins of Human Cancer. Vol. 4, 602 pp.; 77-86; 1977.

The familial risk of breast cancer was studied in relation to a variety of hormone interactions. There was little difference in the physical characteristics or menstrual histories of 49 daughters of breast cancer patients and 46 daughters of control women. However, a bivariate scatter plot of prolactin and follicular phase total estrogen values showed that levels were clearly elevated in 12/34 daughters of patients vs only 1/30 daughters of controls. Luteal phase hormones were also elevated in the former in one study, but not in a second study, and the levels of plasma estrogen, progesterone, and follicle-stimulating hormone (FSH) were elevated in both studies. Nulliparity and a familial risk of breast cancer were increased in bilateral breast cancer patients diagnosed before age 40, and age at first pregnancy was increased in patients diagnosed between ages 40 and 49. Follicular phase estrone and FSH were significantly elevated in 18 daughters of bilateral breast cancer patients. It is concluded that the familial risk of breast cancer is associated with elevated levels of several hormones, including prolactin, progesterone, and estrogen. However, this 'intrinsic' risk is modified by age at first full-term pregnancy. (41 refs.)

78-7163 **Hair Dyes and Human Cancer (Meeting Abstract).** (Eng) Hennekens, C. H. (Channing Lab., Harvard Medical Sch., Boston, MA, 02115); Speizer, F. E.; Rosner, B.; Bain, C.; Belanger, C. *Am J Epidemiol* 108(3): 240-241; 1978. (no refs)

78-7164 **Dietary Correlates of Cancer Risk Among Five Ethnic Groups in Hawaii (Meeting Abstract).** (Eng) Kolonel, L. N. (Biomedical Sciences D-102, Univ. Hawaii, Honolulu, HI, 96822); Nomura, A. N.; Hankin, J. H. *In: Summary Program and Abstracts of Papers. Proceedings of the 3rd Asian Cancer Conference Held by the Philippine Cancer Society under the Auspices of the Asian Federation of Organizations for Cancer Research and Control in Manila, 26-30 September, 1977.* Philippine Cancer Society. (Manila, Philippines): 184 pp.; 81-82; 1977. (no refs)

78-7165 **Seroepidemiologic Assessment of Feline Leukaemia Virus Infection Risk for Man.** (Eng) Krakower, J. M. (Lab. RNA Tumor Viruses, NCI, Bethesda, MD, 20014); Aaronson, S. A. *Nature* 273(5662): 463-464; 1978.

The close environmental association of cats and humans and the known infectivity of feline leukemia virus (FeLV) for human cells in tissue culture prompted the examination of human sera for immunological evidence of exposure to this oncogenic agent. Radioimmunoprecipitation assays for antibodies to the major internal protein (p30) and envelope glycoprotein (gp70) of FeLV were performed with sera from 2,074 individuals, including healthy volunteers, subjects with occupational or home exposure to FeLV-infected cats, laboratory workers with occupational exposure to RNA tumor viruses (including FeLV), and patients with various neoplastic and other disorders. No individual had detectable antibodies against either FeLV protein. Sera from patients with hematologic malignancies and from subjects with known or potential home and occupational exposure to FeLV or FeLV-infected animals were further evaluated in competition radioimmunoassays for p30. None of these persons demonstrated detectable FeLV p30 antigen levels. It is concluded that FeLV infection occurs rarely, if at all, in the population studied. (16 refs)

78-7166 **Cancer Incidence Amongst Cosmetologists (Meeting Abstract).** (Eng) Walrath, J. (Connecticut Cancer Epidemiology Unit, New Haven, CT, 06510). *Am J Epidemiol* 108(3): 234; 1978. (no refs)

78-7167 **Leukemia in Olmsted County, Minnesota, 1965-1974.** (Eng) Linos, A. (Dept. Medical Statistics and Epidemiology, Mayo Clinic, Rochester, MN);

Kyle, R. A.; Elveback, L. R.; Kurland, L. T. *Mayo Clin Proc* 53(11): 714-718; 1978.

An earlier study on the incidence of leukemia in Olmsted County, Minnesota, was extended to include 1965 through 1974. In this decade, the overall crude annual incidence rate was 9.5/100,000. The male:female ratio was 2.4:1, and the incidence rate in men was significantly higher than that in women, especially in the older age groups. Adjusted for age and sex, the mean annual incidence rate among men (17.3) was significantly higher than rates reported previously from other areas (ranging from 10.7 to 13), and it had increased significantly during 1935-1974. The increase was most prominent in men aged 50 yr and over, and it was detectable only in the subgroup with acute myelocytic leukemia. The observed number of farmers with leukemia (8) was significantly higher than that expected (2.8). (26 refs)

78-7168 **Epidemiology of Brain Tumors in Children.** (Eng) Gold, E. B. (Johns Hopkins Univ., Baltimore, MD). *Diss Abstr Int B* 39(2): 665; 1978. (no refs)

78-7169 **Serological and Epidemiological Studies on the Relationships of Human Leukemia and Bovine Lymphosarcoma (Meeting Abstract).** (Eng) Donham, K. J. (Inst. Agricultural Medicine, Univ. Iowa, Oakdale, IA, 52319); Berg, J. W.; Sawin, R. S. *Am J Epidemiol* 108(3): 241-242; 1978. (no refs)

78-7170 **A Case-Control Study of Intracranial Meningiomas in Women (Meeting Abstract).** (Eng) Preston-Martin, S. (USC Sch. Medicine, Los Angeles, CA, 90033). *Am J Epidemiol* 108(3): 233-234; 1978. (no refs)

78-7171 **Radiation- and Host-Factors in Thyroid Tumors Following Thymus Irradiation (Meeting Abstract).** (Eng) Shore, R. (New York Univ. Medical Center, New York, NY, 10016); Hempelmann, L.; Pasternack, B.; Woodard, E. *Am J Epidemiol* 108(3): 233; 1978. (no refs)

78-7172 **Latency Analysis in an Occupational Study of Stomach Cancer (Meeting Abstract).** (Eng) Blum, S. B. (Univ. North Carolina, Chapel Hill, NC, 27514); Smith, A. H.; Andjelkovich, D.; Tyroler, H. A. *Am J Epidemiol* 108(3): 239; 1978. (no refs)

78-7173 **Mortality Among Laundry and Dry Cleaning Workers (Meeting Abstract).** (Eng) Blair, A. (Environmental Epidemiology Branch, NCI, Bethesda, MD, 20014); Decoufle, P.; Grauman, D. *Am J Epidemiol* 108(3): 238; 1978. (no refs)

78-7174 **Cancer Mortality and Agricultural Activity: An Association With Cotton Production and Large Farms in the Southeastern United States (Meeting Abstract).** (Eng) Clark, L. (Univ. North Carolina, Chapel Hill, NC, 27514); Shy, C. M.; Portier, K. M.; Most, B. M.; Florin, J. W. *Am J Epidemiol* 108(3): 242; 1978. (no refs)

78-7175 **Cancer Mortality in Selected Louisiana Parishes and Drinking Water Source (Meeting Abstract).** (Eng) Gottlieb, M. (Tulane Univ., New Orleans, LA, 70112). *Am J Epidemiol* 108(3): 232; 1978. (no refs)

78-7176 **Diet and Cancer of the Colon (Meeting Abstract).** (Eng) Graham, S. (SUNY at Buffalo, Buffalo, NY, 14261); Mettlin, C. *Am J Epidemiol* 108(3): 241; 1978. (no refs)

78-7177 **'Adult Type' Cancer in Children and Adolescents.** (Eng) Pratt, C. B. (St. Jude Children's Res. Hosp., P.O. Box 318, Memphis, TN, 38101); Johnson, W. W.; Hustu, H. O. *In: Third International Symposium on the Detection and Prevention of Cancer held by the International Study Group for the Prevention and Detection of Cancer in New York, April 26-May 1, 1976.* International Study Group for the Prevention and Detection of Cancer (New York, NY): Vol. 1(part 1): 1193 pp.; 961-970; 1977.

The incidence of "adult type" cancer was investigated among 1,009 children with malignant solid neoplasms admitted to a pediatric oncology center between March 1962 and January 1976. Fifty-eight of these patients, aged 3 mo to 19 yr, had tumors usually encountered only in adults. The median age of the 58 patients was 12 yr 9 mo; 22 were Caucasian boys, 18 Caucasian girls, 11 black boys, and 7 black girls. Thirty-seven patients had carcinomas (12 colon, 5 hepatocellular, 3 adrenal, 3 melanoma, 2 pancreas, 2 dysgerminoma, 2 teratocarcinoma, and 1 case each of parotid, thyroid, cholangiohepatocellular, kidney, rectum, seminoma, choriocarcinoma, and adamantinoma). Twenty-one patients had sarcomas (9 liposarcoma, 5 synovial, 2 schwannoma, 2 alveolar soft part, and 1 case each of histiocytoma, angiosarcoma, and mesenchymoma). During the same time period, 960 children were seen with acute lymphocytic leukemia, and 269 with nonlymphocytic leukemia. Among the solid tumor patients, 150 had Hodgkin's disease, 142 neuroblastoma, 127 non-Hodgkin's lymphoma, 99 Wilms' tumor, 99 rhabdomyosarcoma, 74 osteosarcoma, 75 Ewing's sarcoma, and 51 retinoblastoma. There is no indication that more pediatric

atients are being referred with adult-type cancers. However, he admission of nine patients with carcinoma of the bowel ithin a 15-mo period suggests an increasing frequency of is tumor among pediatric patients. Although almost all tuors that are more commonly seen in adults may occur in ildren, the occurrence of these rare tumors is of potential portance in regard to the implications of the changing iagnostic categories of patients referred to pediatric oncoloy centers. (17 refs)

8-7178 **Gallbladder Disease and Gallbladder Cancer among American Indians in Tricultural New Mexico.** (Eng) Morris, D. L. (Univ. Texas Sch. Public Health, Houston, TX); Buechley, R. W.; Key, C. R.; Morgan, M. V. *Cancer* 42(5): 2472-2477; 1978.

The incidence and mortality rates of gallbladder disease and gallbladder cancer were determined for American Indians (A-I), Spanish-Americans (S-A), and Anglo-Americans (A-A) in New Mexico using the data from the New Mexico Tumor Registry. The results confirmed previous reports of an extremely high incidence of gallbladder disease and cancer in A-I. Cases from the registry were used as numerators, data from the 1970 New Mexico population census as denominators; age adjustment was performed using the US standard million. Male mortality from noncancerous gallbladder disease was 15.3 for A-I and 2.8 for AA; the S-A were intermediate at 4.1. The distribution was similar for women. Computed gallbladder cancer incidence rates indicated a 15-fold increase for A-I vs A-A women, and a similar 6-fold increase in men. Again, S-A had intermediate rates. Standard incidence ratios were calculated for these groups, and indicated the magnitude of the differences between these populations. For A-A men and women, the ratios were 72.7 and 66.7, respectively. Analogous figures for A-I and S-A were 463.6 and 1,004.8, and 200.0 and 500.0. Several risk factors, including parity, obesity, age, cholesterol level, and genetic factors, were explored. Genetic factors appeared to be the most important, with parity a contributing factor. Thus, A-I may have a strong genetic disposition toward gallbladder disease and gallbladder cancer. This hypothesis might also explain the high rates in S-A, a high percentage of which have Indian ancestors. (20 refs)

78-7179 **Occupational Dermatoses in the Uranium Industry.** (Cze) Sevcova, M. (Kozni oddeleni, ZUNZ UP, 269 00 Pribram-Zdabor, Czechoslovakia). *Prac Lek* 30(4): 138-141; 1978.

The incidence of dermatoses was not increased in uranium industry workers, but the incidence of basal cell carcinoma was 3.6/10,000 (10.2/10,000 for >5 yr exposure) vs an expected incidence of 0.8/10,000. (13 refs)

78-7180 **Effect of a High Beef Diet on Bacterial Flora and Chemical Components of Human Feces: a Summary of Results.** (Eng) Hentges, D. J. (Univ. Missouri-Columbia, Columbia, MO); Burton, G. C.; Flynn, M. A.; Franz, J. M.; Gehrke, C. W.; Gerhardt, K. O.; Maier, B. R.; Tsutakawa, R. K.; Wixom, R. L. *In: Third International Symposium on the Detection and Prevention of Cancer held by the International Study Group for the Prevention and Detection of Cancer in New York, April 26-May 1, 1976.* International Study Group for the Prevention and Detection of Cancer (New York, NY): Vol. 1(part 1): 1193 pp.; 693-706; 1977.

To examine the effect of a diet high in beef on the bacterial and chemical composition of the feces of humans, 10 male student volunteers were placed on a 4-mo diet series consisting of a control diet, a meatless diet, a high-meat diet, and a second control diet, each of 1-mo duration. The diets were carefully formulated to standardize calories, proteins, fat, carbohydrates, cholesterol, fiber, minerals and vitamins. The fat and fiber content were held constant in all four diets. Total protein was the same in the control and meatless diets but was doubled in the high-meat diet. During the last week of each diet, three fecal samples were collected under oxygen-free conditions from each of the volunteers and analyzed for aerobic and anaerobic bacteria, proximates and minerals, individual amino acids, creatine and creatinine, tryptophan metabolites, polyamines, fatty acids, and neutral and acid steroids. Results showed that there was some increase in the proportion of anaerobic to aerobic bacteria in the feces during the high-meat diet, compared with the meatless diet. There was no increase in the concentration of neutral or acid steroids, and although the high-meat diet contained more cholesterol than did the meatless diet, significantly less cholesterol and fewer cholesterol metabolites were excreted during the high-meat regimen. The results fail to confirm the differences in flora composition and steroid concentration that have previously been observed between populations at high and low risk for colon cancer. (15 refs)

78-7181 **Methodologic Issues in Epidemiologic Studies of Endometrial Cancer and Exogenous Estrogen.** (Eng) Hulka, B. S. (Dept. Epidemiology and Biostatistics, Sch. Public Health, Univ. North Carolina, Chapel Hill, NC, 27514); Hogue, C. J.; Greenberg, B. G. *Am J Epidemiol* 107(4): 267-276; 1978.

Methodologic issues relevant to epidemiologic studies in general and to studies of the association between endometrial cancer and exogenous estrogen intake are discussed. Problems common to all epidemiologic studies concern pathologic misclassification of disease status; determination of the proper type, source, and amount of data to collect; studies of indications for therapy vs studies of the therapy as the cause of the disease; and differences in medical care in different populations. There are also problems associated with the prolonged follow-up of large numbers of patients and with deter-

mination of the appropriate population source from which to estimate the expected incidence of disease. Cohort studies may be biased by the fact that the two patient groups are not necessarily alike with respect to all possible confounding variables. Case-compeer studies have provided the primary epidemiologic basis for the current concern over increased risk of endometrial cancer associated with exogenous estrogen use. These studies involve matching endometrial cancer patients selected from community hospitals with noncancer or "other cancer" patients at the same hospitals or with ostensibily normal community women. They present problems in determining if the study cases are representative of all cases of the disease and in choosing a suitable comparison group from hospitals, the community, hysterectomized vs nonhysterectomized women, or women undergoing a common diagnostic procedure. The potential risk associated with estrogen use must also be weighed against possible benefits; this topic cannot be addressed by case-compeer studies. (23 refs)

78-7182 **Low-Level Radiation and Cancer Deaths.** (Eng) Sanders, B. S. (5823 Soledad Road, La Jolla, CA, 92037). *Health Phys* 34(6): 521-538; 1978.

The incidence of cancer among 17,600 men and 3,900 women who worked at the Hanford Works atomic plant in Richland, Washington, and were exposed to low levels of radiation was determined. For exposed men hired between 1944 and 1971, the mean radiation dose increased progressively from 142 millirems (mrem; rem = roentgen-equivalent-man) in 1944 to 3,745 mrem in 1972; the percentage of deaths from cancer was 19.85 for 1944-1959 and 20.27 for 1960-1972. For those hired in 1944 and 1945, the observed dose gradient rose from 142 mrem in 1944 to 3,762 mrem in 1972; the percentage of cancer deaths was 20.67 for 1944-1959 and 19.10 for 1960-1972. From the time of hire to October 1972, the percentage of deaths from cancer was 20.36 for men hired between 1946 and 1971 and 20.05 for those hired in 1944 and 1945. For each year, the mean dose level of those who died from cancer was not significantly different from the mean of those who died from other causes. The mean dose level for the majority of those who died in a specific year was lower than the mean for survivors in the year of death or in the 1 or 2 yr preceding the year of death. Similar findings were observed among the female employees. Although male employees with radiation exposure had a higher proportion of cancer deaths than the general male population in the state of Washington, there was no indication that the radiation was the cause of this difference. Further studies of exposed men vs nonexposed male employees, and out-of-plant controls indicated that the exposed employees had a greater longevity than identified siblings of such employees, nonexposed employees, and matched controls. Thus, all observations to date indicate no adverse health effects among employees that can be attributed to occupational radiation exposure within permissible limits. (17 refs.)

78-7183 **Measurement of Environmental Nitrosamines.** (Eng) Cohen, J. B. (Natl. Enforcement Investigations Center, Office Enforcement, U.S. Environmental Protection Agency, Denver, CO); Bachman, J. D. *IARC Sci Publ* (19): 357-372; 1978.

The results of a sampling program designed to identify sources of direct emission of nitrosamines (NA's) into the environment and to assess environmental formation of NA's are presented. Samples were taken during summer and winter in the proximity of industrial plants, primarily sources of amines, and analyzed for NA's. There was little indication of the presence or formation of N-nitroso compounds in the air in the vicinity of the sources examined, even when these compounds were observed in plant wastewater. The wastewater samples indicated that N-nitroso compounds are present in chemical, pesticide, and coke plant effluents, some persistently. The in situ sampling did not present any evidence to substantiate secondary production in the vicinity of amine sources. There were no data that would indicate the formation of NA's in the environment, as opposed to their presence as a contaminant. Samples collected along and transverse to major highways showed no contribution of NA's from engine exhaust. The presence of NA's in deionized water (introduced by the mixed-bed resins used for deionization) constitutes a potential, long-term risk for the general population. (9 refs)

78-7184 **Dietary Aflatoxins and Human Primary Liver Cancer.** (Eng) Peers, F. G. (Tropical Products Inst., 56-62 Gray's Inn Road, London WC1X 8LU, England); Linsell, C. A. *Ann Nutr Aliment* 31(4/5/6): 1005-1018; 1977.

The combined results of two studies, one performed in the Murang'a district of Kenya and the other in Swaziland, show a high degree of positive correlation between calculated ingestion levels of aflatoxin, expressed as nanograms/kilogram/day (x), and the adult incidence rates of hepatocellular carcinoma, expressed as cases/10^5 adults/year (y). This positive correlation is true for both men and women. Based on an assumed 2-kg/day intake of wet diet a a mean body wt of 70 kg, the calculated relationship for adult women is: $y = 4.14 \log_{10}x - 0.80$. With the added assumption of a daily intake of 2 liters/day of native beer, the regression equation for adult men is: $y = 21.96 \log_{10}x - 11.17$. These regression data are essentially compatible with comparable data recorded by independent workers in Thailand and Mozambique, the latter being the region where the highest rates of liver cancer and the highest aflatoxin ingestion levels have been recorded to date. A highly significant regression line was also calculated using crude liver cancer incidence data and aflatoxin exposure levels from all available studies: $y = 7.60 \log_{10}x - 3.60$. (27 refs)

-7185 **Variable Globin Chain Synthesis in Mouse Erythroleukemia Cells.** (Eng) Alter, B. P. (Div. ematology and Oncology, Children's Hosp. Medical Cen-, 300 Longwood Ave., Boston, MA, 02115); Goff, S. C. *ood* 52(5): 1047-1057; 1978.

arious mouse erythroleukemia cell (ELC) lines were treated th chemical inducers to determine the proportion of β inor globin (β-MG) synthesis. When cultured with 2% methylsulfoxide, cell lines 745 and 707 from DBA/2 mice nthesized 25%-48% β-MG (75%-52% β-major globin). duction of the same cells with butyric acid (1 millimole) d to approx 40% β-MG production, but induction with emin (75 μM) resulted in $>80\%$ β-MG synthesis. ELC nes derived from other mouse strains show variations in the roportions of globin chains, compared with those from BA/2 mice, when subjected to similar treatment. The nemical inducing agents did not influence protein stability the initiation of globin synthesis. Translation of poly -containing cytoplasmic RNA in a wheat germ-free system sulted in the same proportions of β-MG as those seen in tact cells. It is concluded that the induction of globin production depends on the specific interaction of erythroid precursors with the inducing agents and is due to the regulation of transcription, differential posttranscriptional stabilization of messenger RNA, or the selective proliferation of cells whose specific type of globin production is predetermined. (37 refs)

See also:
*(Rev.): 78-6634, 78-6637, 78-6641, 78-6642, 78-6644, 78-6646, 78-6648, 78-6649, 78-6651, 78-6652, 78-6653, 78-6659, 78-6662, 78-6664, 78-6667, 78-6680, 78-6684, 78-6685, 78-6696, 78-6697, 78-6698, 78-6699, 78-6700, 78-6701, 78-6703.
*(Chem.): 78-6709, 78-6710, 78-6712, 78-6720, 78-6765.
*(Phys.): 78-6803, 78-6804, 78-6829, 78-6833, 78-6838.
*(Viral): 78-6905, 78-6951, 78-6961.
*(Immun.): 78-6980, 78-7035, 78-7036, 78-7066.
*(Path.): 78-7096, 78-7097, 78-7107, 78-7127.

78-7186 **Compartmental Modeling and Analysis for Carcinogenic Experiments.** (Eng) Whitmore, R. W. (Texas A & M Univ., College Station, TX, 77843). *Diss Abstr Int B* 39(4): 1854; 1978. (no refs)

78-7187 **Further Studies on Liver Glyoxalase I and Glyoxalase II. Activity in Mice Bearing Sarcoma 180 and L1210 Leukemia.** (Eng) Winter, R. (Inst. Biology and Physiology, Silesian Medical Acad., 41 808 Zabrze, Poland); Piskorska, D.; Jerzykowski, T. *Neoplasma* 25(4): 465-470; 1978.

Glyoxalase I and II activities were determined in the livers and tumor cells of BDF_1 and DBA_2 mice bearing implanted sarcoma 180 and L1210 leukemia in ascites form. The ascites fluids had been injected into the peritoneal cavity. No glyoxalase II activity was detected in the cells of either tumor, but glyoxalase I activity was reduced in comparison with that in normal tissues. Hepatic glyoxalase I and II activities decreased progressively during tumor development. This reduction was as high as 40%-60% of the initial levels. The results corroborate previous findings on the absence or reduction of glyoxalase activity in tumor cells and in the liver during tumor development, and they indicate that a tumor developing ip affects glyoxalase activity in the liver, an organ not directly attacked by the tumor. (23 refs)

78-7188 **Impaired Regulation of Activity of Cell Membrane Adenylcyclase and Guanylcyclase as Possible Factor of Carcinogenesis.** (Rus) Khermann, B. (Dept. Internal Medicine, Emil Weil Hosp., Budapest, Hungary). *Vopr Onkol* 24(10): 28-31; 1978.

A discussion is presented of the implications of the recently discovered enzymatic imbalance in the cancer cell. The prevalence of catabolism over anabolism in the tumor cell confirms the hypothesis that the impaired metabolism of the tumor cell can be measured in terms of changes in the balance of activity of adenylcyclase vs activity of guanylcyclase. (14 refs)

78-7189 **A Comparison of Polysomal Messenger Ribonucleoprotein Particles from Normal and Neoplastic Rat Liver.** (Eng) Cardelli, J. A. (Dept. Oncology, McArdle Lab. Cancer Res., Medical Sch., Univ. Wisconsin, Madison, WI, 53706); Pitot, H. C. *Cancer Res* 38(7): 2099-2102; 1978.

Free polysomes were isolated from normal and regenerating rat liver and from Morris hepatomas 7777, 7800, 5123C, and 9618A and compared in terms of their messenger ribonucleo protein particles (MRP). Sucrose gradient analysis ruled ou the possibility of any significant messenger RNA (mRNA degradation in these polysome preparations, since the poly somes were relatively large (8-12 ribosomes/mRNA) and th tissues contained only small amounts of disomes. Th EDTA-disrupted polysomes were fractionated on oligodeox ythymidylic acid-cellulose columns. The column-boun polyriboadenylic acid-containing MRP were eluted with formamide buffer, precipitated with ethanol, and subjecte to polyacrylamide gel electrophoresis in the presence of sodi um dodecyl sulfate. The mRNA-associated proteins from th different tissues were qualitatively similar, but two protein with a mol wt of 66,000 and the 109,000, which were found as minor proteins in normal liver, appeared on gels as majo protein bands when hepatoma MRP were examined. The two proteins were also minor proteins in regenerating and hos liver MRP, suggesting that their increase in the hepatoma was not due to tissue growth or to exposure to an altered hormonal environment per se. The possibility exists that the increase in certain MRP is related in some way to the initiation and/or maintenance of the neoplastic state. (15 refs)

78-7190 **Analysis of RNA Initiated in Isolated Mouse Myeloma Nuclei Using Purine Nucleoside 5′[γ-S] Triphosphates as Affinity Probes.** (Eng) Smith M. M. (Dept. Molecular Biology, Univ. Edinburgh King's Buildings, Mayfield Road, Edinburgh, Scotland EH9 3JR); Reeve, A. E.; Huang, R. C. *Cell* 15(2): 615-626; 1978.

The purine ribonucleoside triphosphate analogs adenosine 5′[γ-S]triphosphate and guanosine 5′[γ-S]triphosphate were used as affinity probes to study RNA chain initiation in isolated nuclei from the mouse myeloma 66.2 cell line. The binding was specific and dependent on inclusion of the sulfur nucleotide analogs in the in vitro synthetic reaction. The affinity-labeled RNA appeared to be initiated in vitro. The nuclei incorporated 1.2-2.4 picomoles of uridine monophosphate/10^6 nuclei/min, and the rate of synthesis was unaffected by substitution of the nucleotide analogs for the normal nucleotides. The percentage of total RNA synthesized that was incorporated into sequences initiated in vitro was 7.8%-9.6%. The size of the total RNA synthesized ranged from <5S to 45S, and the size of the affinity-labeled sequences ranged from <5S to 28S. The incorporation into RNA initiated in vitro was abolished by α-amanitin in concentrations inhibitory for polymerase II or III. Over 70% of the total incorporation into ribosomal 5S RNA transcripts was into sequences initiated in vitro. This initiation was catalyzed by polymerase III and was specific for guanosine triphosphate as the initiating nucleotide. The RNase T1 fingerprint of the newly initiated 5S RNA indicated that this gene was accurately initiated and elongated in vitro. (52 refs)

-7191 **Circulating DNA and Oncogenesis.** (Eng) Anker, P. (Div. Oncohaematology, Dept. Medicine, ɔpital Cantonal, Geneva, Switzerland); Stroun, M.; Mauɛ, P. *In: Third International Symposium on the Detection d Prevention of Cancer held by the International Study oup for the Prevention and Detection of Cancer in New rk, April 26-May 1, 1976.* International Study Group for : Prevention and Detection of Cancer (New York, NY): l. 1(part 1): pp. 1193; 3-16; 1977.

e DNA released from eukaryote cells (reDNA) was chaɛterized, and the possible existence of circulating DNA was ɔlored. The material released from frog auricles and from man blood lymphocytes had the UV absorption characterics of cellular DNA and was 95% digested by DNase but ensitive to RNase and pronase. The mol wt of the reDNA s not as homogeneous as that of cellular DNA: the latter d one peak over 18S, but reDNA had two main peaks of out 12S and 7S. Separation on CsCl gradients indicated at the AT/GC ratio was the same for both DNA's. The DNA was not due to a DNA loss from damaged cells, and ere was constant renewal of extracellular DNA with each ange of medium, suggesting that release is governed by a ecise homeostatic mechanism. The DNA was released in a mplex containing proteins, among which were enzymes cessary for partial extracellular synthesis of reDNA. Near- t neighbor analyses showed that this extracellular synthesis as a true synthesis. The spontaneous transfer of DNA from cterial to higher organisms that occurs during bacterial fection and its subsequent transcription might be a general ological process that occurs between eukaryote cells in norɛal conditions, and it suggests the existence of circulating NA. In view of the fact that DNA extracted from maligɛnt cells can transform normal cells, an oncogenic role of rculating DNA is postulated. It is possible that a circulating NA may not necessarily be transforming but might be inɔlved in changes associated with malignancy. (29 refs)

8-7192 **In Vitro Cell Proliferation Studies in Hodgkin's Disease.** (Eng) Cowley, J. G. (Natl. Inst. Onɔlogy and Radiology, Havana, Cuba). *Neoplasma* 25(1): 3-90; 1978.

)NA replication in lymph node cells from 30 untreated Iodgkin's disease patients was studied autoradiographically sing two different tritiated thymidine pulse-labeling techiques. Nine patients with inflammatory reactive conditions erved as controls. The results confirmed previous labeling ata, but they showed that DNA synthesis can also be detectɛd among the reticulum cells. Cell proliferation in Hodgkin's nd Reed-Sternberg cells appeared to be a characteristic of arge mononuclear elements even though some multinuclear lements were detected in DNA synthesis. Large multipolar nitoses were frequent in the Hodgkin's patients, which sugɛested that the multinuclear cells may have evolved from the nononuclear cells. (17 refs)

78-7193 **Super-sensitive DNA-Repair Test-Liquid for Confirming DNA-Damagicity of Mutagens (Meeting Abstract).** (Eng) Nishioka, H. (Doshisha Univ., Kyoto, Japan). *Mutat Res* 53(2): 242-243; 1978. (1 ref)

78-7194 **Coordinated Regulation of Octopine Degradation and Conjugative Transfer of Ti Plasmids in *Agrobacterium tumefaciens*: Evidence for a Common Regulatory Gene and Separate Operons.** (Eng) Klapwijk, P. M. (Dept. Biochemistry, State Univ. Leiden, 2300 RA Leiden, Netherlands); Scheulderman, T.; Schilperoort, R. A. *J Bacteriol* 136(2): 775-785; 1978.

In an attempt to determine whether octopine utilization is genetically related to conjugative *Agrobacterium tumefaciens* Ti plasmid transfer by the functioning of a shared regulatory mechanism and whether there is a correlation between the genes responsible for octopine metabolism and tumorigenesis, the analog noroctopine was used to isolate *A. tumefaciens* mutants with altered regulatory patterns for Ti plasmid-associated degrading genes. Results of cointegration, conjugation, and octopine oxidase and permease enzyme assays revealed three distinct mutant groups: (1) those with a constitutive level of octopine enzymes and a high degree of spontaneous Ti transfer; (2) those with high enzyme levels but not transfer; and (3) those in which both conjugation and octopine utilization were induced by noroctopine. It was concluded that these results were due to the activity of a common gene. Additionally, when homo-octopine was used to produce mutants defective in octopine metabolism, strain virulence was dependent on the ability to transfer the Ti plasmid. The results indicate that conjugative transfer does not play a significant part in crown gall tumor induction in plants. (38 refs)

78-7195 **Use of the Betabinomial Distribution When Testing for Weak Mutagenic Activity in the Dominant-Lethal Test (Meeting Abstract).** (Eng) Vuataz, L. (Mathematics Section, Nestle Products Technical Assistance Co. Ltd., 1814 La Tour de Peilz, Switzerland); Sotek, J. *Mutat Res* 53(2): 281; 1978. (2 refs)

78-7196 **Mutagenicity Testing by Automated Measurement of Colony Growth and Morphology (Meeting Abstract).** (Eng) Glaser, D. A. (Dept. Molecular Biology and Virus Lab., Univ. California, Berkeley, CA, 94720); Konrad, M. W. *Mutat Res* 53(2): 192; 1978. (no refs)

78-7197 **Mitogens for Murine Embryo Cell Lines.** (Eng) Herschman, H. R. (Sch. Medicine, Univ. California, Los Angeles, CA, 90024); Passovoy, D. S.; Pruss, R. M.; Aharonov, A. *J Supramol Struct* 8(3): 263-268; 1978.

The growth-promoting activites of fetal bovine serum, cortisol, phorbol myristate acetate (PMA), prostaglandin F2, insulin, epidermal growth factor (EGF), and fibroblast

growth factor (FGF) were evaluated in four murine embryo cell lines (Swiss 3T3, BALB 3T3, M2, and C3H10T1/2). All cell lines showed an increased saturation density when grown in progressively higher serum concentrations, but the M2 cell line demonstrated a somewhat reduced response to serum in comparison with the other three lines. The results were variable: positive results for most mitogens ranged from 50% to 100% increases in cell numbers. PMA was mitogenic for both Swiss 3T3 and M2 cells but not for 10T1/2. Prostaglandin F2 was mitogenic only for Swiss 3T3 cells, but cortisol was inactive in all four lines. Insulin was stimulatory only for Swiss 3T3 cells, and then only at very high concentrations when compared with other polypeptide mitogens. A 50% increase in saturation density occurred in Swiss 3T3 cells in response to 1 ng/ml of EGF, whereas a similar growth response was elicited only with 1,000-10,000 ng/ml insulin. At 100 ng/ml, EGF resulted in mitogenic responses of 172%, 284%, 127%, and 312% in Swiss 3T3, Mw, C3H10T1/2, and BALB 3T3 cells, respectively. At 10 ng/ml, FGF caused increases of 144%, 121%, 85%, and 122% in the respective cell lines; at 100 ng/ml the corresponding values were 217%, 199%, 122%, and 171%. These experiments show that serum, EGF, and FGF stimulate cell division in all four lines, albeit to varying degrees for the different target cells. (23 refs)

78-7198 **Sulfated Mucopolysaccharides from Normal Swiss 3T3 Cell Line and Its Tumorigenic Mutant ST1: Possible Role of Chondroitin Sulfates in Neoplastic Transformation.** (Eng) Dietrich, C. P. (Departamento de Bioquimica e Farmacologia, Escola Paulista de Medicina, Caixa Postal 20372, Universidade de Sao Paulo, Brazil); Armelin, H. A. *Biochem Biophys Res Commun* 84(3): 794-801; 1978.

The surface sulfate mucopolysaccharides (MPS) of normal Swiss 3T3 cells and a glucocorticoid-sensitive Swiss 3T3 tumor mutant (ST1) were compared. MPS were labeled by incubation with $Na_2{}^{35}SO_4$ (10 μCi/ml), cultured, trypsinized, and analysed by agarose gel electrophoresis and enzymatic degradation with appropriate enzymes. Normal 3T3 cells contained primarily chondroitin sulfate B (CSB) (49% in whole cells) and heparin sulfate (HS) (40%), plus small amounts of CSA (11%). The ST1 mutant contained chondroitin sulfate A (CSA) (43%), HS (44%), and small amounts of CSB (13%). After the addition of hydrocortisone to ST1 cell cultures, the cells showed some of the properties of normal cells (cell density, anchorage, and serum dependence), but their sulfated MPS composition remained constant. Degradation of normal and ST1 cells with chondroitinases B and ABC showed that they contained only 4-sulfated disaccharides. Normal Swiss 3T3 and 3T6 cells, both of which undergo spontaneous transformation with time in culture, showed increased CSA and decreased CSB after exhibiting phenotypic characteristics of transformation, including loss of contact inhibition. These results support the hypothesis that glucuronic acid-containing CSA A plays a role in the stimulation of cell division in neoplastic and embryonic sues. (19 refs)

78-7199 **Establishment and Characterization of a N Human Urinary Bladder Carcinoma Cell L (PS-1).** (Eng) Sanford, E. J. (Div. Urology, Dept. Surge Milton S. Hershey Medical Center, Pennsylvania State Ur Coll. Medicine, Hershey, PA, 17033); Geder, L.; Dagen, E.; Laychock, A. M.; Ladda, R.; Rohner, T. J. *Invest U* 16(3): 246-252; 1978.

An epithelioid cell line (PS-1) was established from a hum transitional cell carcinoma of the urinary bladder. Sc inj tion of the epithelioid cells into weanling athymic nude m induced solid tumors histologically similar to the original mor. A cell line was also established from a tumor induc in an athymic nude mouse (PS-1, T-1). Both cell lines exhib ed essentially identical growth characteristics and formed monolayer growth of epithelioid cells in culture. Electron m croscope studies confirmed the epithelioid morphology. fibroblastoid elements were observed. Chromosomal analy revealed heteroploidy with persistent marker chromosom all cells contained a Y chromosome. The presence of mor-specific antigen(s) in PS-1 cells was suggested by m crocytotoxicity assays with peripheral allogeneic ly phocytes from other transitional cell cancer patients. Sera urinary bladder cancer patients reacted with nuclear antige of the established cells. (22 refs)

78-7200 **Serum Ribonucleases in Pancreatic Cancer: R lation to Tumor Histology.** (Eng) Funakoshi, (Third Dept. Internal Medicine, Faculty Medicine, Kyus Univ., 1-1 Maeda-shi 3-chome, Higashi-ku, Fukuoka Ci 812, Japan); Wakasugi, H.; Kimura, T.; Matsumoto, M Ibayashi, H. *Gastroenterol Jpn* 13(5): 390-394; 1978.

Serum ribonuclease (RNase) levels of 18 normal persons, patients with chronic pancreatitis, and 26 patients with pa creatic cancer were determined using polycytidylic as su strate. The RNase levels of patients with four histologic typ of pancreatic cancer were compared, ie, in patients with du tar cell adenocarcinoma, and anaplastic cell, acinar cell, a islet cell carcinoma. The normal level of serum RNase w 92 ± 6.3 units (U). In chronic pancreatitis and pancrea cancer it was 118 ± 10.4 and 249 ± 16.8 U, respectivel Patients with ductar cell adenocarcinoma had the highe serum RNase levels. The phosphocellulose chromatograph patterns of the serum RNase and pancreatic cancer tum extract were compared with those of serum RNase and pa creatic extracts from normal subjects. Control serum a control pancreatic extract both exhibited three main eluti patterns, but pancreatic cancer serum and tumor extract e hibited a different elution pattern and high activity. It is su gested that enzyme elevations may be due to the synthes of a new species of RNase and an increased enzyme synthes by the proliferating tumor cells. If this theory proves correc early diagnosis of pancreatic cancer may be accomplished b analyzing serum RNase isozymes. (13 refs)

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